

and I listened

Body Language: When writing about the revealed and

and surgical

the hidden, the voiced and the silent, physicians

let her write

add dimension, character, and humanness

and posture

to their profession, their patients, and themselves

rejoice; you

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gives body language
voice and perspective.

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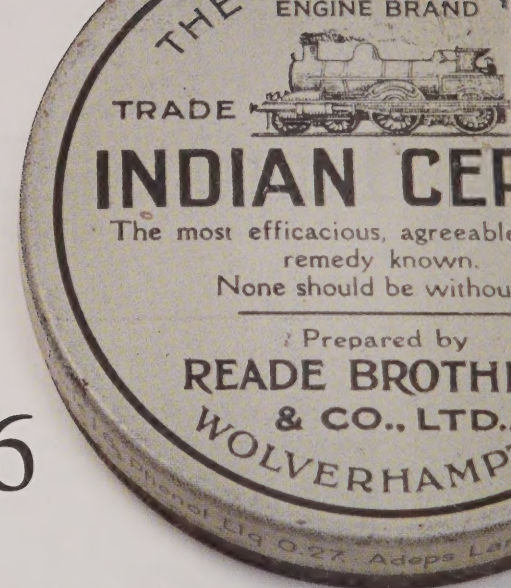
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From the Dean

THOUGHTS ON INNOVATION



PHYSICIANS ARE TRANSLATORS who spend their days interpreting the sounds, shapes, and textures of the human body. Little wonder, then, that so many of us turn to words—to stories—to explain and understand our profession.

The stories patients tell us are our daily fare. Almost without realizing it, we use these stories as tools to guide us as we make decisions to order a test, recommend a specialist, or prescribe a therapy. Outside of the clinic, we continue to rely on stories to bear witness to what we have encountered: quantitative stories in journals, qualitative stories during rounds and with colleagues, confessional stories to ourselves.

This issue of *Harvard Medicine* investigates body language, telling the stories of medicine and medical research. Cells, for example, are given voice by scientists who've spent years listening to and translating their chemical messages, while the science behind baby babble, perhaps our earliest efforts to tell stories, takes shape through birdsong. Listening in on clinic conversations, we explore the nuance and metaphor of regionalisms while separately reflecting on the healing power that words can have for physician, patient, and student.

Finally, we turn to our alumni for stories that present the poignancy and privilege of our profession. We celebrate those stories in "Body Language," an essay of story and art.

I hope this issue of *Harvard Medicine* speaks to you.

A handwritten signature in blue ink, appearing to read "Jeffrey S. Flier".

Jeffrey S. Flier

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Harvard Medicine is published three times a year at 25 Shattuck Street, Boston, MA 02115.

Publishers: Harvard Medical Alumni Association and Harvard Medical School

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Third-class postage paid at Boston, Massachusetts. Postmaster, send form 3579 to 107 Ave. Louis Pasteur, Boston, MA 02115. ISSN 2152-9957 • Printed in the U.S.A.

Letters to the Editor

CHART NOTES FROM OUR READERS

Castle Mots

The article “At Their Service” in the Winter/Spring issue of *Harvard Medicine* reminded me of my encounters with the famous William Castle. In my second year of medical school, my class went to Boston City Hospital to hear a lecture by Castle. He entered the lecture hall wearing overalls and carrying a tool kit. He explained that the elevator in the hospital had broken and that the repairman wanted to charge the hospital \$5 an hour to repair it! So Castle had repaired it himself.

I did not meet Castle again until I was in the last two months of my fourth year. My wife and I had received a phone call at our basement apartment. “This is Mrs. Castle,” the caller said. “I’d like to invite you and your wife to dinner at our home.” I thought it was a prank call from one of my married friends’ wives, so I kept asking, “Who is this?” Eventually I took down the date of the dinner and the address.

Preparing for that evening, my wife and I couldn’t decide how to dress. My wife decided to put on her best dress, her hat, and white gloves, and I put on my best suit, shirt, and tie, and shined my shoes. When we arrived, I knew it was Castle’s home: In the driveway was his 1936 Model T Ford that he not only drove but serviced and repaired himself. When we rang the doorbell, Castle answered. He was wearing a pair of dungarees and holding a glass of beer.

At dinner, Mrs. Castle served a delicious chicken potpie, so I said, “Gee, how come we’re not having liver?” Castle had studied the liver and pernicious anemia and had discovered vitamin B12, which proved to be a cure for that type of anemia. Castle laughed at my remark, saying he would never eat liver. As the dinner progressed, I mentioned how we had struggled to select our clothing for the evening and that, thinking the dinner might include a fourth-year quiz, I had studied up on liver disease and pernicious anemia. He laughed and laughed. When we left, he told me he’d had such a good time that he was going to invite a married student and his wife to dinner every year.

Home Brew

When we rang the doorbell, Castle answered. He was wearing a pair of dungarees and holding a glass of beer.

MURRAY STROBER '51
PASSAIC, NEW JERSEY

A few years later, my wife and I were living in one of three rooms in my mother-in-law’s Brooklyn apartment while I interned at SUNY Downstate Medical Center. I was stationed at King’s County Hospital in Brooklyn and was earning \$40 a month. Word had spread that the world-renowned William Castle was visiting his close friend William Dock, also a world-famous professor of medicine, at the Downstate Medical School. Apparently, Castle had asked Dock whether Murray Strober was an intern at the hospital, so, when the two physicians entered the lecture hall where we had gathered to hear Castle speak, Castle saw me, rushed over, and hugged me in front of the whole assembly. I knew then that my application to be resident at King’s County, with a salary rise to \$60 a month, was a sure thing.

MURRAY STROBER '51
PASSAIC, NEW JERSEY

The Winter/Spring issue of *Harvard Medicine* refers to William Castle’s adventures in plumbing repair during his years at Thorndike Memorial Lab. As a hematology

summer student fellow in 1958, working in Castle’s lab with my mentor, Allan Erslev, I had heard that a problem with the water bath for the vitamin B12 assay setup had been causing crashes of its *Euglena* population.

Now, neither *Euglena* nor vitamin B12 was my strong suit. Just two years earlier, however, I had concluded my three years aboard an aircraft carrier with a hitch as repair division officer. That meant I was the officer in charge of the ship’s plumbers. So when I heard about the problem with the water bath, I looked under the sink and found a cross connection between the hot and cold water systems. Eureka! The erratic temperature of the water bath was explained. My action endeared me to Castle, and he publicly complimented me. I felt I had earned my 10 seconds of hematologic fame.

JAMES R. HUGHES '60
FAIRLEE, VERMONT

Speed Reading

I found the story “Enduring Pleasures” in the Winter/Spring issue of *Harvard Medicine* personally interesting. For decades, I’ve been active in personal health promotion. I started running at age 43 and became a triathlete at 46. Now in my thirty-second season, I’ve done more than 240 triathlons and duathlons. Also, over the years I’ve written several books on both variants, written many columns for a variety of triathlon periodicals, and contribute to a monthly blog on the USA-Triathlon web site. Most important, I am as excited now to get to the start line—and to cross the finish line—as I was back in 1983. Along with my wife, running centers my life.

STEVEN JONAS '62
EAST SETAUKET, NEW YORK

Harvard Medicine welcomes letters to the editor. Please send letters by mail (Harvard Medicine, 107 Avenue Louis Pasteur, Suite 111, Boston, MA 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity.



* The figures quoted have been checked and certified to by LYBRAND, ROSS BROS AND MONTGOMERY, Accountants and Auditors.

20,679* Physicians
say **"LUCKIES**
are *less irritating*"

PUFF PEACE

Fifty years after the surgeon general's report, clinician-researchers look at efforts to stem tobacco use

THERE WAS A TIME when ashtrays were in every home, smoking was allowed on all airplanes, and hospitals had to deal with the surreptitious influx of off-premises cigarettes. Nearly everyone attending the May 30 Alumni Day Symposium, "Up in Smoke: 50 Years of Policy, Perception, and the Public's Health" remembered that time well. Most of the physicians in attendance admitted they had parents who smoked. But when asked by modera-

tor Steve Schroeder '64, if anyone had a child who smoked, only one hand went up.

A half century after the U.S. Surgeon General published a report on the ill effects of tobacco use on health, "it is not a normal thing to smoke in this country anymore," said Schroeder, who is the Distinguished Professor of Health and Health Care and director of the Smoking Cessation Leadership Center at the University of California, San Francisco. Currently, 18 percent of the U.S. population smokes, down from 42 percent in 1965.

The bad news, however, he added, is that smoking is increasingly a phenomenon among the poor and the poorly educated, and is especially common among people with mental illness or substance use disorders. These populations consume about 40 percent of all cigarettes sold in the nation.

Nancy Rigotti '78, an HMS professor of medicine and director of the Tobacco Research and Treatment Center and associate chief of the Division of General Medicine at Massachusetts General Hospital, discussed physicians' evolving response to tobacco. The thinking on smoking has moved from being considered just a bad habit to being recognized as an addiction and a chronic disease. "Patients are now told they have a problem and need treatment," Rigotti said. "This approach has increased both short-term and long-term abstinence from smoking." With electronic medical records and meaningful-use requirements that call for the identification of those who smoke, "we can now reach out to smokers instead of waiting for them to come to us."

Change has also come in the marketplace. In February, CVS announced it would no longer sell tobacco products, becoming the first national retail pharmacy chain in the country to do this. Andrew Sussman '91, senior vice president and associate chief medical officer of CVS Caremark, said the action was undertaken "to help further diminish tobacco use and make it less socially acceptable." Approximately 1 million of CVS's 5 million daily customers are cigarette smokers. According to Sussman, CVS has found "that doing what's right for patients is also right for business." One poll showed that 25 percent of respondents were more likely to shop at CVS pharmacies following the announcement that the company would stop selling tobacco products. In addition, since the announcement, the stock price of CVS rose almost 20 percent.

—Ellen Barlow



PIN IT: HMS graduates Hayley Walker (left) and Amanda Dilger capture the moment with a selfie.

THE POWER OF COMMUNITY

Class of 2014 graduates encouraged to hew to their vision and values

UNDER CLEAR BLUE SKIES, 200 medical and dental school graduates gathered on the HMS Quad on May 29 with faculty, family, and friends to celebrate the closing of one chapter of their careers and the opening of the next.

Addressing the graduates, keynote speaker Vivek Murthy, an HMS instructor in medicine at Brigham and Women's Hospital, founder of Doctors for America, and the nominee for Surgeon General of the United States, spoke of the importance of personal vision and values as the new graduates navigate their careers, their interactions with patients, and their efforts to improve health care.

"Stand up for your values," said Murthy, "and you can change not only your patients' lives but also

health care in this nation—and the world."

Defining and holding true to your beliefs is not easy, Murthy cautioned. It requires examining different ideas, resisting the temptation to follow other people's paths just because they've already been paved, and holding firm against hardship and opposition.

Now more than ever, Murthy said, the nation and the world need health care practitioners "who can imagine the world as it should be and who have the courage to step forward with open minds, clear eyes, and full hearts to translate those dreams into reality."

In doing so, he promised, today's graduates will inspire others to follow their lead.

Building on the theme of improving the lives of patients, HMS Dean Jeffrey S. Flier assured the graduates that they were well prepared for this responsibility.

"You, as this school's mission attests," said Flier, "are now part of a community known for new ideas and new leadership, each in the service of alleviating suffering and disease."

"This responsibility, this membership in the HMS community, may seem daunting, but it shouldn't. You have been well trained and mentored for this role. You are prepared and you can always draw support from each other, from this school, and from the generations of proud HMS alumni upon whose sturdy shoulders you stand.

"HMS graduates have a deep tradition of amazing accomplishments. I, and our entire faculty, look forward to being astonished by yours."

On this Class Day, 164 students received Doctor of Medicine degrees from HMS, including 44 students who also earned master's or doctoral degrees. In addition, the School awarded Master of Medical Science degrees to 33 students: 12 in the Scholars in Clinical Science program, 9 in the Clinical Investigator Training program, 8 in biomedical informatics, and 4 in the inaugural class of the Global Health Delivery program.

—compiled from articles by Stephanie Dutchen, Susan Karcz, and Jake Miller

Decanal Shift

Redesign of medical education curriculum to be a priority

ON OCTOBER 28, which, appropriately enough, is Medical Education Day at HMS, the School will welcome a new dean for medical education. In July, Jules Dienstag, who for 10 years has overseen the education of more than 1,600 students, announced he would step down from the post. His successor, Edward Hundert '84, now directs the Academy Center for Teaching and Learning, the Academy fellowship in medical education, and the monthly HMS medical education grand rounds. In addition, Hundert is the associate director of the HMS Center for Bioethics and, from 1990 through 1997, served as associate dean for student affairs.

"Ed's multifaceted career has provided him with the perspective and leadership skills needed to build effective teams and to lead HMS through this exciting period of curriculum reform," wrote Dean Jeffrey S. Flier in his announcement to the HMS community. "There are few individuals more qualified to build on the momentum Jules has established."

Flier noted Dienstag's many contributions to HMS, including his leadership of the medical education reform initiative, which produced a new integrated curriculum in 2006. Flier emphasized Dienstag's service to the Program in Medical Education curriculum, noting especially the departing dean's "passion for the School's mission and a deep respect for our students."

Added Flier, "More recently, Jules has convened leaders at HMS to begin working collectively toward a new era of medical education reform, one of my leading priorities. As this reform process moves into its final year before its expected launch, now may be the ideal juncture for a leadership transition, enabling a new dean for medical education to complete the planning and development process, and then shepherd the curriculum over the next five years and more without interruption."

Dienstag will remain at HMS as the Carl W. Walter Professor of Medicine, and will split his time between advisory roles at the School and at Massachusetts General Hospital.



MASS APPEAL

Device used in physics and chemistry reveals dynamics of a pervasive pathogen

IF YOU HAVE IT, you probably don't know it. Cytomegalovirus, or CMV, is perhaps one of the biggest pathogens you've never heard of—big, both proportionately and epidemiologically. It contains approximately 200 genes, compared to HIV's paltry 18, and it's everywhere. Once you have it, you have it for life.

The good news is if you're healthy, it's harmless. The T cells of your immune system keep it in check, and you're none the wiser.

The bad news, however, is if you have a medical condition that dampens your immune system, such as HIV infection or a recent organ transplant, the virus can assert itself with a vengeance. The results, sometimes, are life-threatening.

In the June 5 issue of *Cell*, researchers in the lab of Steven Gygi, an HMS professor of cell biology, report that they discovered a menu of tactical secrets CMV employs. Using mass spectrometry, a tool commonly used in physics and chemistry, the researchers described the dynamics of a CMV infection in a fibroblast, or connective tissue cell, over a three-day course of infection. As a

result, the researchers were able to identify ways CMV evades the immune system and to show how certain viral proteins target and destroy human proteins that defend against infection.

"This is an entirely new way of studying the behavior and tactics of viruses," says Gygi.

Mass spectrometry is usually used to describe and measure small molecules. Inside the tool, molecules are shattered by an electric charge and then brought through a magnetic field where they are characterized one by one.

Traditionally, this tool has not been applicable to the life sciences because biomolecules, such as proteins, are too large for this technique. Over the past 15 years, however, Gygi has been trying new ways of incorporating mass spec into biology. In one approach, known as electrospray, protein subunits are vaporized and then sprayed into a chamber where they are broken apart by helium. The mass spec then sequences the amino acids of each subunit. The molecules are "reassembled" using an algorithm that matches them to a protein database.

Michael Weekes, a postdoctoral researcher in the Gygi lab and an expert in infectious disease, decided to use mass spec for virology and chose CMV. Although widespread, very little is known about the virus.

Weekes took a sample of fibroblasts newly infected with CMV, harvested the proteins from both the virus and the cell, and sprayed them into the mass spec at different times over three days in order to construct a trajectory of infection. The first three days of infection are particularly important for they mark a covert stage during which the virus hijacks the cell, but hasn't yet begun to destroy it.

The researchers were able to study approximately 8,000 proteins, identifying not only ways that CMV evades the immune system, but also discovering a number of new therapeutic targets. Most notably, they were able to look closely at proteins that live on the cell surface. These proteins are of great interest: Most drugs target them, yet, because cell surface proteins are few in number, they are harder to study than intracellular proteins are.

Weekes and his colleagues found 29 viral proteins living on the cell surface, 23 of which had not previously been discovered. Many of these CMV surface proteins deter immune cells. Others block cellular proteins that activate immunity. In other words, CMV wards off rescuers while disabling a cell's ability to defend itself.

"So much of this viral genome is dedicated to simply evading the immune system," says Weekes.

The next step, according to the researchers, would be to identify antibodies against many of these viral proteins and, ideally, to destroy infected cells before they can replicate and spread the pathogen.

—David Cameron



Shirk de Soleil

Research in mice connects UV light to opiate-like effects

WITH THE DANGERS OF ULTRAVIOLET LIGHT EXPOSURE so well recognized, why has it been so hard to convince people to avoid time in the sun? A new study from HMS investigators at Massachusetts General Hospital bolsters one theory: ultraviolet (UV) light is addictive.

Using a mouse model, the scientists found that chronic UV exposure raises circulating levels of beta-endorphin and that UV-habituated animals exhibit withdrawal symptoms if beta-endorphin activity is blocked. The study, led by David Fisher, the Edward Wigglesworth Professor of Dermatology at HMS and Mass General, was reported June 19 in *Cell*.

Part of the skin's natural response to UV light is the production of a protein called POMC, which is then clipped into several fragments, one of which induces production of the pigment melanin. Processing of a different segment of POMC leads to the generation of beta-endorphin in the skin. Fisher's study investigated whether this UV-induced beta-endorphin produces opioid-like effects such as pain relief and dependency. The study also examined whether the pathway mediating these effects is initiated by the production of endorphin in the skin.

By exposing the test animals to a daily dose of UV light calculated to induce tanning but not burning of the animals' skin, the scientists found that, after one week, the levels of beta-endorphin in the animals' blood rose significantly, remained elevated during the exposure period, then gradually returned to normal after UV exposure was discontinued. Tests conducted at regular intervals during the study period showed that the UV-treated animals were less responsive to light touch or temperature changes than a control group with no UV exposure. The higher the animals' beta-endorphin levels, the less sensitive they became. But administration of naloxone, which broadly blocks opioid-pathway activity, returned skin sensation to normal in the UV-treated animals.

In UV-habituated animals, naloxone treatment also produced such classic symptoms of opioid withdrawal as trembling, shaking, and teeth chattering. In contrast, a strain of mice in which POMC production was selectively blocked or that lacked the beta-endorphin gene altogether exhibited none of the responses or symptoms seen in UV-exposed normal mice, confirming the presence of a UV-activated opioid pathway in the skin.

—Sue McGreevey

Bubble Vision

Possible new option for opening and closing the blood-brain barrier

LIKE A BOUNCER at an exclusive nightclub, the blood-brain barrier allows only select molecules to pass from the bloodstream into the fluid bathing the brain. Nutrients get in; toxins and pathogens don't. The barrier also ensures that waste products are filtered out of the brain and whisked away.

Although the barrier helps maintain the delicate environment necessary to the human brain's health, there is a problem: the barrier is so discerning, it won't let medicines in. Researchers haven't been able to coax it open, either; they don't yet know enough about how the barrier forms or how it functions.

Now, an HMS team has identified a gene in mice, *Mfsd2a*, which may be responsible for limiting the barrier's permeability, and has found that the molecule it produces, Mfsd2a, works in an

unexpected way. Their study was published online May 14 in *Nature*.

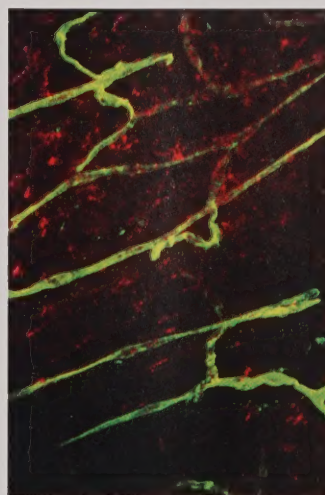
Most attempts to understand and manipulate blood-brain barrier function have focused on tight junctions that prevent all but a few substances from squeezing between barrier cells. Chenghua Gu, an HMS associate professor of neurobiology, and her research team discovered that Mfsd2a appears to affect transcytosis, a little-studied process in which substances travel through the barrier cells in bubbles called vesicles. Transcytosis occurs frequently at other sites in the body but is normally suppressed at the blood-brain barrier. Mfsd2a may be one of the suppressor agents.

"It's exciting. This is the first molecule identified that inhibits transcytosis," says Gu. "It opens up a new way of thinking about how to design strategies to deliver drugs to the central nervous system."

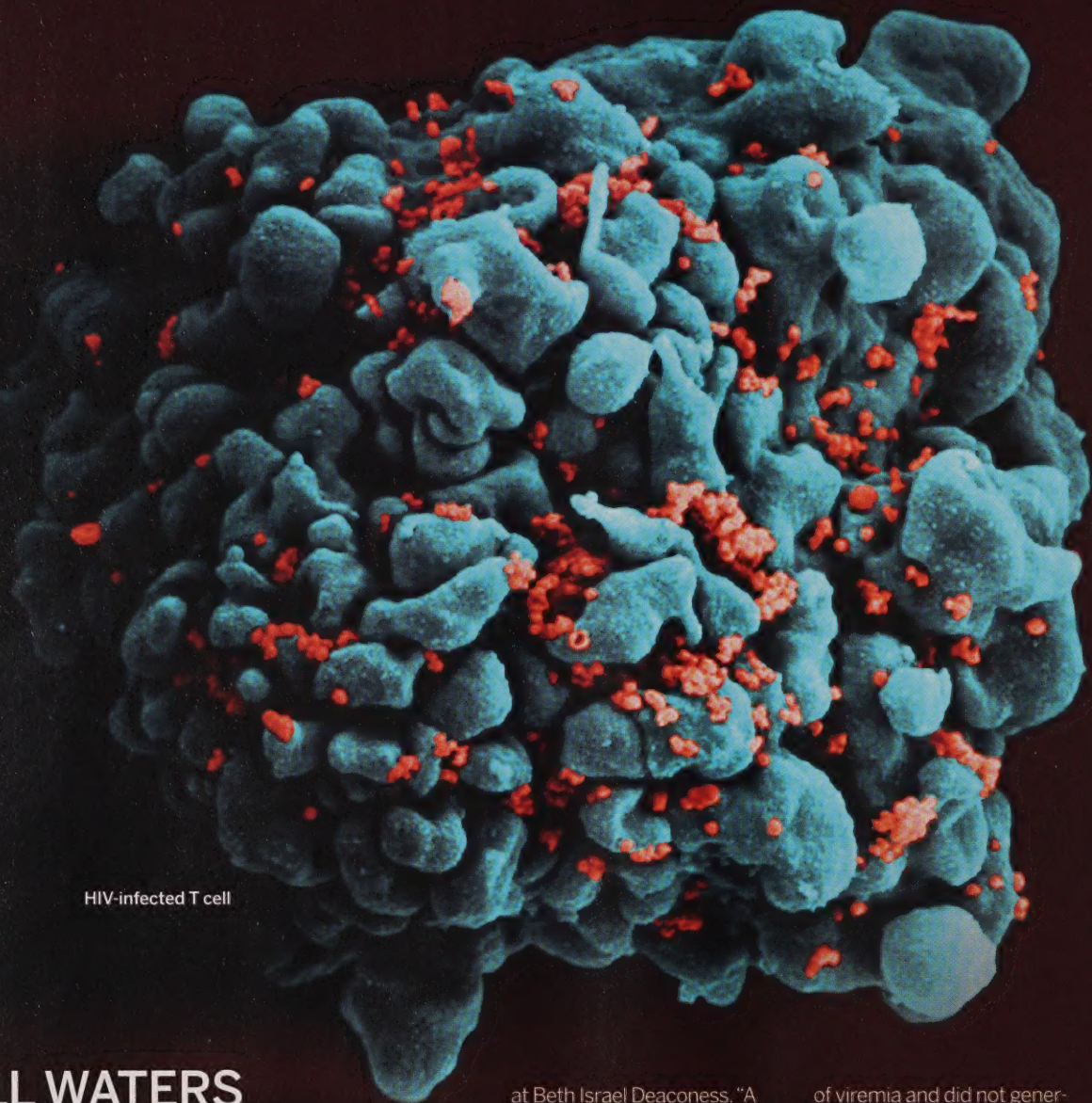
Mfsd2a has a human equivalent, so controlled blocks to its activity could allow the passage of drugs that treat life-threatening conditions in humans such as brain tumors and infections.

Conversely, because researchers have begun to link blood-brain barrier degradation to several brain diseases, boosting Mfsd2a or the molecule it produces might help strengthen the barrier and perhaps alleviate diseases such as Alzheimer's, multiple sclerosis, and amyotrophic lateral sclerosis. The findings may also have implications for other areas of the body that rely on transcytosis, such as the retina and kidney.

—Stephanie Dutchen



RED FLAG: Capillaries (green) without *Mfsd2a* leaked red tracer dye, revealing the gene's role in blood-brain permeability.



HIV-infected T cell

STILL WATERS

Discovery presents new challenges for HIV eradication efforts

A VIRAL RESERVOIR of HIV-1, the umbrella term for the cells in which the virus lies dormant and out of reach of antiretroviral drugs, represents the most critical barrier to the development of a cure for HIV-1 infection. Very little has been uncovered about when and where a viral reservoir, also known as a latent reservoir, is established during acute HIV-1 infection, or the extent to which it is susceptible to early antiretroviral therapy (ART).

Now, in a study published online July 20 in *Nature*, a research team led by investigators at Beth Israel Deaconess

Medical Center report that a viral reservoir is established strikingly early after intrarectal simian immunodeficiency virus (SIV) infection of rhesus monkeys and before detectable viremia. For this work, the Beth Israel Deaconess scientists collaborated with colleagues in the U.S. Military HIV Research Program.

"Our data show that a viral reservoir was seeded substantially earlier after infection than was previously recognized," says team leader Dan Barouch '99, an HMS professor of medicine and director of the Center for Virology and Vaccine Research

at Beth Israel Deaconess. "A reservoir was established in tissues during the first few days of infection, before the virus was even detected in the blood."

This discovery coincides with recent reports of the resurgence of HIV in the "Mississippi baby," who was thought to have been cured by early administration of ART. "This unfortunate news further emphasizes the need to understand the early and refractory viral reservoir that is established quickly following HIV infection in humans," adds Barouch.

In this new study, the team administered ART to groups of monkeys on days 3, 7, 10, and 14 after intrarectal SIV infection. Animals treated on day three showed no evidence

of viremia and did not generate any SIV-specific immune responses. Nevertheless, all of the animals in the study exhibited viral resurgence when treatment was stopped after six months.

"The seeding of a viral reservoir within the first few days of infection presents new challenges to HIV-1 eradication efforts," says James Whitney, an HMS instructor in medicine at the Center for Virology and Vaccine Research at Beth Israel Deaconess, and lead author of the study. "Our data suggest that extremely early initiation of ART, extended ART duration, and probably additional interventions that activate a viral reservoir will be required for HIV-1 eradication."

—Bonnie Prescott

Gut Reaction

Research on early-onset inflammatory bowel disease may help young sufferers

INFLAMMATORY BOWEL DISEASE is miserable for anyone, but when it strikes a child under age five, it's also quite severe, usually causing bloody diarrhea, wrenching abdominal pain, and stunted growth. Early-onset IBD is rare but, for unknown reasons, is on the rise, with its incidence increasing by about 5 percent annually in some parts of the world.

A recently identified form of early-onset IBD shows up within months of birth, causing severe inflammation in the large intestine and abscesses around the anus. Recently linked to genetic mutations in the cellular receptor for the signaling protein interleukin-10 (IL-10), it can also lead to lymphoma later in life.

As with all early-onset IBD, IL-10-receptor deficiency has no effective treatment. A bone marrow transplant is a cure but carries many risks, especially for infants.

"We've been trying to understand why IBD in these children is so severe and presents so early," says Dror Shouval, an HMS clinical fellow in pediatrics at Boston Children's Hospital. The beginnings of such an understanding, reported by Shouval, as lead author, and colleagues in the May 15 issue of *Immunity*, could lead to a new treatment approach for this and perhaps other kinds of early-onset IBD.

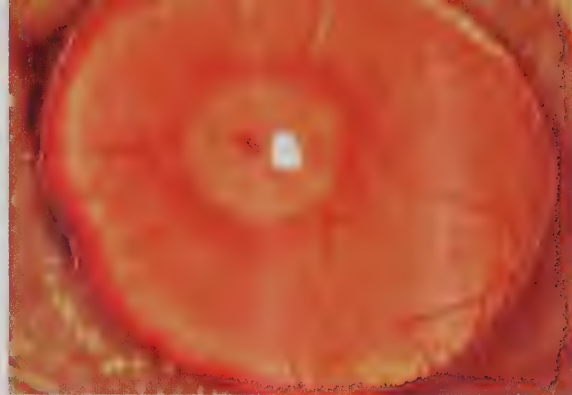
Working through its receptor, IL-10 quiets inflammatory immune responses during periods when there's no threat of infection. Working with mouse models, the researchers showed that when innate immune cells near the intestine didn't receive IL-10 signals, the mice lost weight and developed rapid, severe intestinal inflammation. They also found that without the ability to sense IL-10, the mice could churn out pro-inflammatory macrophages but produced comparatively few having anti-inflammatory properties. The macrophages they did produce functioned poorly. As a result, the murine immune systems also produced fewer, and less well-functioning, T-regulatory cells, another type of calming immune cell.

Simply put, their intestinal immune responses were out of whack.

The researchers then tapped a worldwide patient cohort study of early-onset IBD, identified seven children from as many countries who manifested IBD and IL-10-receptor mutations, and studied their disease in the laboratory. The results mirrored those found in the mouse model.

The mouse studies had another, more hopeful, finding. By transferring anti-inflammatory macrophages into the IL-10-receptor-deficient mice, the researchers were able to ameliorate their IBD.

—Nancy Fliesler



Second Sight

Adult human stem cells show promise for corneal regrowth

A MOLECULE known as ABCB5, which acts as a marker for hard-to-find limbal stem cells of the eye, may offer a means for restoring vision by enhancing regrowth of human corneal tissue, say HMS researchers. Their research, which used a mouse model, is the result of a collaboration between the Massachusetts Eye and Ear/Schepens Eye Research Institute, Boston Children's Hospital, Brigham and Women's Hospital, and the VA Boston Healthcare System. The findings may help people who have been blinded by chemical injury, burns, and eye diseases.

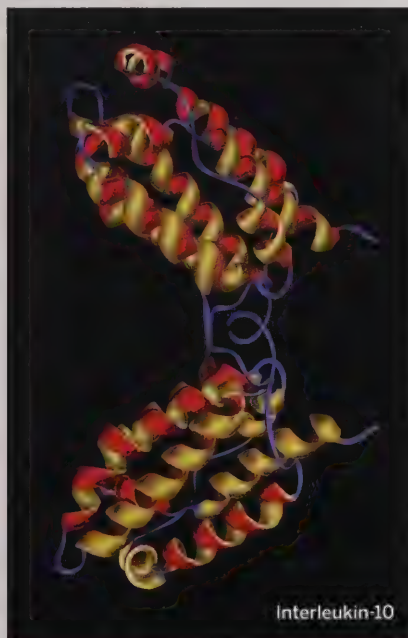
The research, published in the July 7 issue of *Nature*, also describes the construction of tissue from an adult-derived human stem cell.

Limbal stem cells reside in the eye's basal limbal epithelium, or limbus, and help maintain and regenerate corneal tissue. Their loss due to trauma or disease is one of the leading causes of blindness. In the past, tissue or cell transplants have been used to help the cornea regenerate, but the presence and number of actual limbal stem cells in the grafts has been uncertain and the outcomes of the grafts have been inconsistent.

"Limbal stem cells are rare, and successful transplants are dependent on these rare cells," says Bruce Ksander, an HMS associate professor of ophthalmology at Mass Eye and Ear, who co-lead the study. "This finding will now make it much easier to restore the corneal surface."

Markus Frank, an HMS assistant professor of pediatrics at Boston Children's, and Natasha Frank, an HMS assistant professor of medicine at Brigham and Women's, who were co-senior investigators on the study, had previously discovered ABCB5 in tissue precursor cells in human skin and intestines. In the mouse model used for this study, they found that ABCB5 also occurs in limbal stem cells and is required for their maintenance and survival, and for corneal development and repair. Mice lacking a functional ABCB5 gene lost their populations of limbal stem cells, and their corneas healed poorly after injury.

—Nancy Fliesler and Mary Leach



Interleukin-10



FISHING TRIP

New compound may stem cardiac condition that can cause sudden death

a NEW DRUG COMPOUND isolated from zebrafish may reverse arrhythmogenic cardiomyopathy, say HMS researchers at Beth Israel Deaconess Medical Center and Brigham and Women's Hospital. Their finding, reported in the June 11 issue of *Science Translational Medicine*, may one day lead to new therapies for this condition.

Arrhythmogenic cardiomyopathy, or ACM, is a hereditary disease. The condition affects approximately 1 in 5,000 individuals worldwide, and is the leading cause of sudden death in young people under age 35.

Over time, the disease damages the muscle of the heart's ventricles, causing the muscles' cells, or myocytes, to be replaced by fatty deposits and fibrosis. These changes leave patients especially susceptible to arrhythmias, the rapid and erratic heartbeats that cause dizziness, collapse, and, in the most serious cases, sudden cardiac death.

"There are currently no drugs available that can reliably prevent arrhyth-

mias and sudden death in ACM," says team leader Jeffrey Saffitz, the HMS Mallinckrodt Professor of Pathology and chair of the Department of Pathology at Beth Israel Deaconess. Patients who exhibit frequent arrhythmias or experience repeated fainting spells are considered to be at risk for sudden death, and often undergo implantation of a cardiac defibrillator, which continuously monitors heart rhythm and delivers a shock to the heart if it detects a potentially lethal rhythm abnormality.

To identify the mechanisms underlying this dangerous condition and to find potential drugs to prevent its onset, the research group created a screenable zebrafish model of ACM with cardiac myocyte-specific expression of a human mutation in the gene encoding plakoglobin, which is known to cause ACM in humans. (Zebrafish develop rapidly so the investigators could see clear evidence of heart disease after only 48 hours of embryonic development.) The scientists then screened thousands of chemicals to find any that could suppress the disease. One chemical, SB216763, showed a remarkable ability to prevent or reverse the disease in the fish.

—Bonnie Prescott



Myeloma in human pelvis

Package Delivery

Nanoparticle drug-delivery system shown effective in bone-cancer model

USING A MOUSE MODEL of myeloma, a type of bone cancer, scientists at HMS tested a nanoparticle drug-delivery system they engineered from clinically safe biodegradable polymers and alendronate, a bisphosphonate-based therapeutic agent for cancer, and found the targeted therapy to be effective, capable not only of killing tumor cells but also of stimulating growth of healthy bone tissue.

The research, the result of a collaboration between investigators at Brigham and Women's Hospital and Dana-Farber Cancer Institute, was reported in the June 30 issue of the *Proceedings of the National Academy of Sciences*.

For the study, the research team injected mice with nanoparticles loaded with bortezomib, an anticancer drug. Then they introduced myeloma cells into the animals. The scientists found that the nanoparticles, aided by the alendronate, homed in on the bone tissue and delivered their drug cargoes, killing the tumor cells.

Alendronate played a dual role in this engineered system. Bisphosphonates bind to calcium, and since the largest store of calcium in the human body is in bone, the bisphosphonates accumulate in high concentration in bones. In addition, bisphosphonates are commonly used in the treatment of cancers that metastasize to the bone.

The research team found that the treatment slowed myeloma growth and prolonged survival. Moreover, they found that bortezomib changed the makeup of bone, enhancing its strength and volume.

"These findings suggest that bone-targeted nanoparticle anticancer therapies can deliver a concentrated amount of drug in a controlled and target-specific manner capable of preventing tumor progression in multiple myeloma," says Omid Farokhzad, an HMS associate professor of anaesthesia and director of the Laboratory of Nanomedicine and Biomaterials at Brigham and Women's, and the study's co-senior author. "This approach may prove useful in treating bone metastasis, common in 60 to 80 percent of cancer patients, and in treating early stages of multiple myeloma."

—Marjorie Montemayor-Quellenberg

Unintended Consequences

Decline in therapeutic use of antidepressants linked with rise in teen suicide attempts

RESEARCHERS HAVE FOUND that U.S. Food and Drug Administration safety warnings about a potential increase in risk for suicide associated with the therapeutic use of antidepressants among young people may have inadvertently led to an increase in suicide attempts by teens and young adults.

The 2003 warnings generated widespread media coverage that precipitated a sudden steep decline in the number of prescriptions for antidepressants without any offsetting increases in other effective treatments. In a study reported online June 18 in *BMJ*, researchers at the HMS Department of Population Medicine and the Harvard Pilgrim Health Care Institute write that in the second year after the warnings, antidepress-

sant use fell by more than 30 percent among adolescents, coupled with a relative increase of approximately 22 percent in the use of psychotropic drugs to attempt suicide. Among young adults, the decrease in antidepressant use two years after the warnings was slightly more than 24 percent, while the relative increase in suicide attempts approached 34 percent in this group.

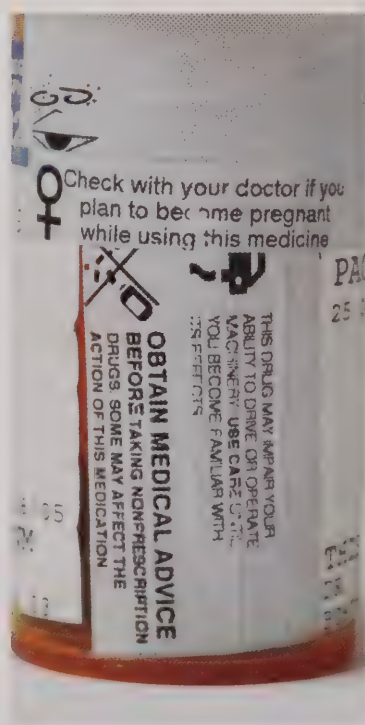
The researchers used overdose with psychotropic drugs as a conservative measure of suicide attempts. The number of completed suicides, however, did not change for any age group studied.

In 2003, an analysis that combed through existing clinical trials noted that approximately 1 percent of adolescents and young adults taking antidepressants experienced an increase in suicidal ideation. The original warning mentioned only this potential risk without noting the potential risk of undertreating depression. According to the researchers, the warnings alarmed clinicians, parents, and young people, and many prominent media outlets mentioned that these drugs raised the risk of suicide.

The FDA later revised the warning to recommend that physicians weigh the risk of prescribing the medication against the risk of not prescribing the medication, and that doctors monitor patients for thoughts of suicide and treat them as needed.

"This study is one of the first to directly measure a health outcome driven by the interaction of public policy and mass media," says Christine Lu, an HMS instructor in population medicine at Harvard Pilgrim Health Care Institute and study leader.

—Jake Miller



AUSCULTATION

LISTENING IN ON MEDICAL EDUCATION



In It Together

Bonds between physicians may be key to weathering the storms of change
by Zirui Song

I BELONG TO A GENERATION of physicians who will enter practice at a time when the health care system is undergoing profound change. Many states are expanding insurance coverage. Insurers are changing the way medical care is reimbursed. Hospitals are consolidating. And physicians across specialties are facing new incentives to integrate care to keep populations healthy.

In addition to these changes, my generation faces a professional environment that requires more teamwork, more coordination, and a stronger sense of shared vision. No matter what specialties we choose, we will increasingly work within large health care systems

that require physicians and allied health professionals to collectively manage the health of their patient populations within a budget.

Although many obstacles stand in the way of improving our health care system, every day I witness examples of col-



laboration. As a medical student, I saw team huddles in outpatient clinics that brought providers together around high-risk patients. I saw multispecialty rounds inside the hospital that molded multiple recommendations into an ideal care plan. Then in April of last year, while on a surgical rotation at Faulkner Hospital, I saw perhaps the most powerful and inspiring instance of unity in medicine.

While scrubbing in on a case with my resident and attending, our pagers began to go off. Eleven patients who had been injured in the Boston Marathon bombings arrived minutes later. In the hours that followed, I saw raw determination and shared purpose on the faces of physicians and nurses around me. Their responses were spontaneous, and they were profound. On that day, the collective desire to help those in need—and one another—overwhelmed any divisions in our medical world.

Today, opinions differ over the challenges our profession faces—and how to solve them. As health care costs continue to drive our national debt higher, pressure to slow its growth increasingly falls to my generation of physicians. More than ever, society is asking for transparency and accountability from our profession. As medical students on the wards, we heard talk of an uncertain future. From some physicians, we heard of the rationale behind payment and delivery-system changes. From others, we heard of the pitfalls and frustrations that such changes would bring. Two-thirds of physicians in the United States today believe that health care costs are somebody else's problem to fix, not one that they themselves should fix.

My generation of physicians will be asked to take a leadership role in addressing health care costs. Medical bills are the leading cause of personal bankruptcy in this country. Companies cut wages in order to pay for workers' medical care. States cut funding for schools and for food aid because of health care spending. For our patients, our colleagues, and our society, setting our health care system on a fiscally sustain-

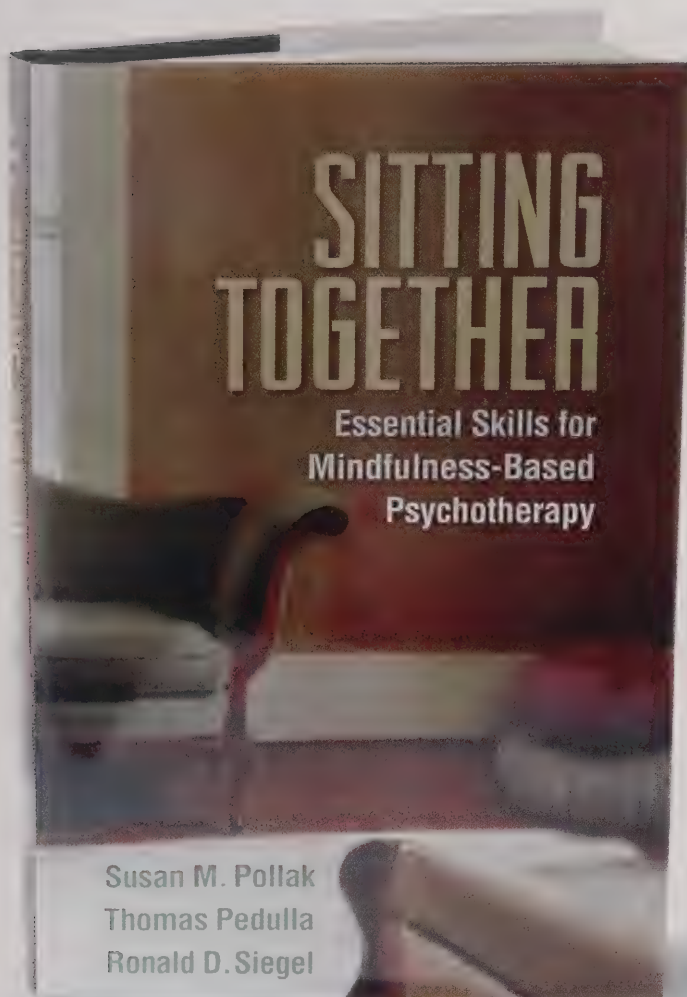
able path is a task worthy of our attention.

We will enter practice in more than 100 specialties and subspecialties. In a world where the human body has been divided into turfs, we will be asked to stitch the turfs back together. We will face new payment systems that compensate us collectively, as organizations of providers, rather than as individual practitioners. And, as with compensation, we will be asked to share risks collectively, rather than individually. The quality of our work will also be measured collectively. In short, our generation of physicians is in it together.

Navigating this change will require us to take care not only of our own patients but also of each other. Our collective accountability for cost and quality makes teamwork across specialties a core physician skill. Listening to each other, compromising with each other, and nurturing one another will be essential as our profession moves forward.

An ethos core to medicine is that the patient-physician relationship is sacred. We need to recognize that the physician-physician relationship is equally sacred. The age of health care reform may come and go, but its legacy might just be in the reminder that becoming a physician is a uniquely collegial privilege.

Zirui Song '14 is a resident in internal medicine at Massachusetts General Hospital. In 2012, Song earned a PhD in health policy (economics track) from the Graduate School of Arts and Sciences at Harvard University. In January, Forbes magazine featured him in its annual "30 Under 30" series on promising young scientists and entrepreneurs in health care.



BREATHING LESSONS

Sitting Together: Essential Skills for Mindfulness-Based Psychotherapy
by Susan M. Pollak, Thomas Pedulla,
and Ronald D. Siegel

(GUILFORD PRESS, 2014)

reviewed by Elissa Ely

JUST WHAT IS THIS "MINDFULNESS," this word Buddhists and therapists love to use, this word that's on the tongue of the twenty-first century everywhere, this overused, misunderstood word?

The authors of *Sitting Together: Essential Skills for Mindfulness-Based Psychotherapy* have spent years on the question. In their book, Susan Pollak, Thomas Pedulla, and Ronald Siegel, all psychotherapists and longtime meditators, manage to be sensible and inspirational at the same time. It's like levitating by sitting still.

They start, as we should, at the beginning. Mindfulness, the meditative "awareness of present-moment experience with acceptance," has been around in some form for 2,500 years. Life is not easy, but it can be easier than we often make it. Even without full understanding, most therapists can recommend the benefits of mindfulness for anxiety and depression.

Yet—be honest, busy helpers—how many of us meditate? The therapist who prescribes but doesn't practice mindfulness is like the internist who gives health advice while lighting up.

And so, the book begins with exercises that build our skills: first, in focusing attention, then in monitoring responses with neutrality (they use a lovely image of sitting by a quiet pool where "all sorts of creatures come to drink before they move on"), and finally, in acting with equanimity.

The authors understand the hazards of eager, quickly disillusioned beginners and warn us wryly about "lurching prematurely toward absolute truth." They also understand our sheepish imperfections. There are guided meditations for distractedness ("an experienced therapist can nod, ask for clarifications...and appear to demonstrate understanding, all while planning a 12-course meal"), compassion fatigue, second-hand trauma, and even patient no-shows.

Once they've helped us become more calm and attentive, the authors turn to our patients, with "suggestions from the laboratory of the clinical hour." Mindfulness-based psychotherapy rests on diagnosis, formulation, and individual treatment planning, just like any therapy should.

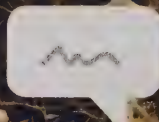
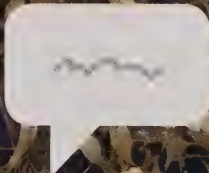
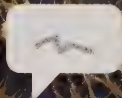
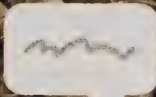
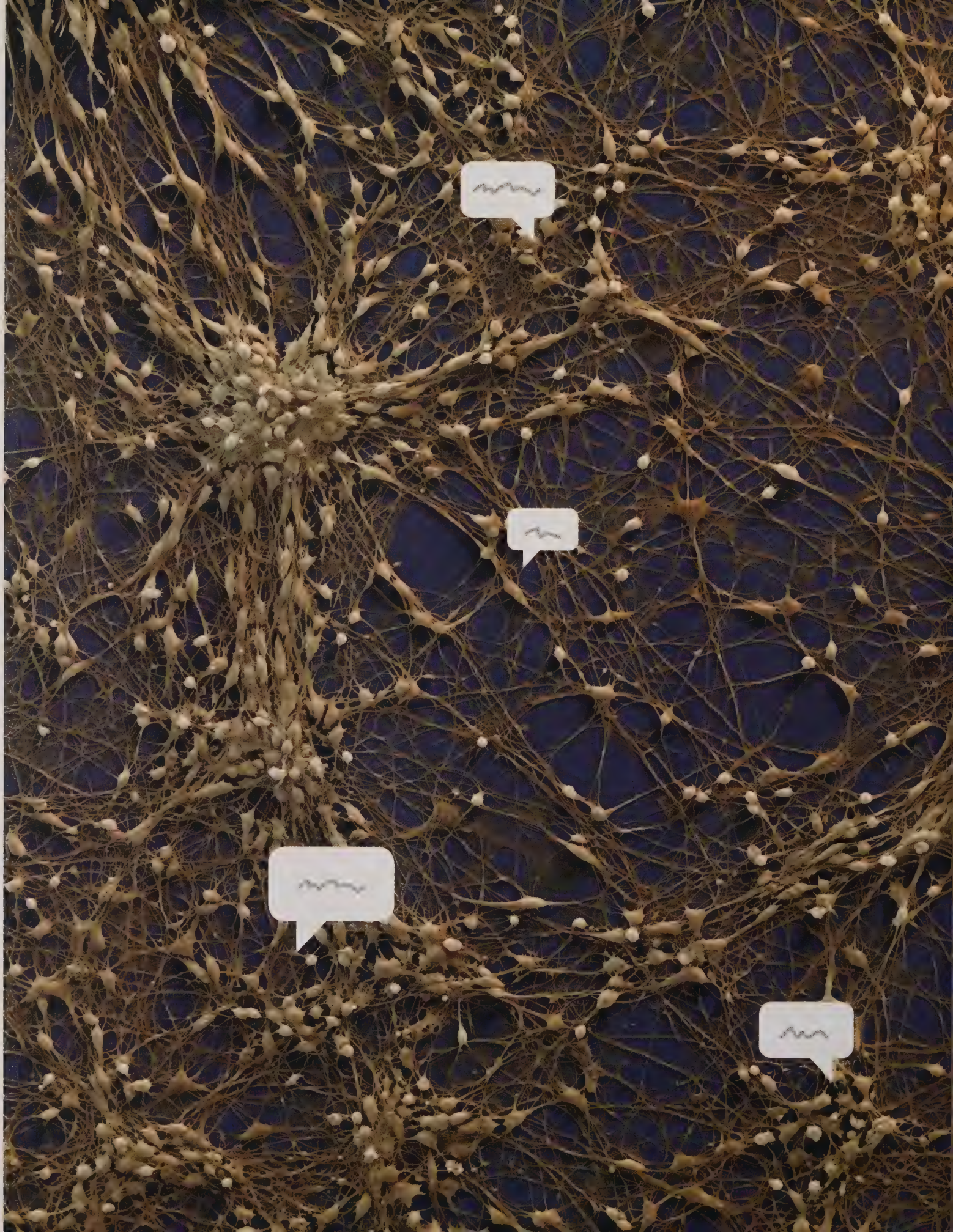
Here's where their skills are truly persuasive. There are illustrations of several cases—and one breathtaking example of a long and complex trauma treatment—built on a ladder of meditative techniques they call "the art of sequencing." Early on, their traumatized patient was unable to sit at all, so walking meditation was used. Focusing on breath was too intimate, so the patient learned to concentrate on peripheral parts of the body. Storms of emotion were overwhelming, so she practiced a meditation that allowed distance between the feeling and the feeler. Each stage of treatment was personalized with a theoretical frame and with exercises.

The patient climbed the ladder unsteadily, and in so doing, grew steadier. "Ladder" is my improper metaphor, though, because there is no top step. "Termination," the writers point out, "is a bit of a misnomer, for... work on oneself never ends."

Free downloads and handouts are available at the end of *Sitting Together*, heartfelt signs of a desire to help. A warning to skeptics: there is also a chapter that touches on the possibility of higher spiritual purposes. But this is done lightly, "If we perceive that we have moved beyond the traditional territory of psychotherapy," the authors mull, "can we bill insurance?"

Mindfulness is nothing if not accepting. The authors realize that one response from patients, and therapists too, will be doubt. But that's no problem. Even doubters have to breathe sometime.

Elissa Ely '87 is a psychiatrist at the Massachusetts Mental Health Center.





Internal Dialogues

If we take the time to listen, our bodies' cells have quite a bit to say **by Stephanie Dutchen**

The chef shouts for more of the day's specials. Immediately, certain line cooks start chopping onions while others heat oil on the stove. One cook nudges his neighbor for the salt. A sous-chef finishes plating salads and rings a bell. A waiter appears and ferries the plates into the dining room. ■ If the human body were a kitchen, its cells would be the chefs, wait staff, diners, and busboys that perform all the specialized tasks required to keep the organism running smoothly—only there would be 200 kinds of cells doing different jobs. ■ The key to successful functioning? Communication. If cells didn't talk

to one another, human bodies wouldn't be able to see, hear, breathe, think, move, or do anything at all. ■ "Every aspect of an organism's function depends on some kind of communication," says Joan Brugge, the Louise Foote Pfeiffer Professor of Cell Biology at HMS. ■ Whether it's a group of insulin-producing cells calling for everyone to take up more sugar from the bloodstream, or a stem cell murmuring to its neighbors that they should become cartilage while those guys over there become muscle, intercellular communication tells every cell what to be, what to do, where to go, when to reproduce, and when to die.

It's not surprising, then, that almost everything that goes wrong in our bodies can be traced to a failure of communication. Cells can go deaf, as in type 2 diabetes when they don't respond to insulin. They can go mute, as in type 1 diabetes when pancreatic cells don't release insulin at all. Cells can send the wrong message or misinterpret a correct one, speak up at inappropriate times, or act when they haven't been told to.

Scientists have been trying to learn the ancient language of cells for more than a hundred years, eager to deepen the knowledge of how our bodies work.

Unfortunately, despite great progress, "We're not yet fluent," says John Flanagan, a professor of cell biology at HMS. "We can go to a restaurant, but we might order the wrong item. We can't have a conversation."

Flanagan anticipates a time when doctors and researchers can "listen in on what's going wrong in a certain disease and then be able to direct change. We could say with confidence, 'I want these cells to stop dividing.'"

Every time cell biologists think they're close to understanding the syntax of the human body, the details seem to get more complicated. But with each passing year, Flanagan, Brugge, and others learn more about the conversations that keep our bodies running and devise new methods to eavesdrop on and interrupt diseases such as cancer. Their work takes us another step toward becoming conversant in our cells' languages.

Are You Talking to Me?

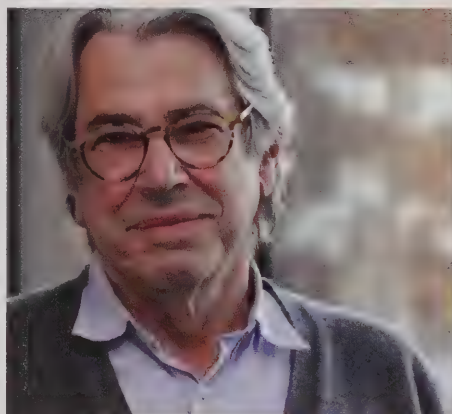
Adrian Salic's immune cells are communicating more than he'd like.

Pollen particles that Salic has inhaled have sounded an alarm. Mast cell-bound immunoglobulin E antibodies have begun to latch on to the particles and to call for reinforcements. Other proteins leap into the huddle until finally the mast cells burst, spilling out histamine and other inflammatory substances.

In other words, Salic, an HMS associate professor of cell biology, has seasonal allergies.

He rubs his eye. "One way to think of cell communication," he says, "is as a set of languages with many dialects."

Cell A talks by releasing a chemical signal in, say, Russian. The signal travels a predetermined distance and reaches Cell B, which can be next door or at the far end of the body.



CALL CENTER: Discovering the languages of cells and translating cell-to-cell conversations have been central to the research of (clockwise, from lower left) Spyros Artavanis-Tsakonas, Joan Brugge, Adrian Salic, and John Flanagan.

Cell B hears the message because it has receptors on its surface that fit the signal's highly specific molecular shape: It's got an ear for Russian. It relays the signal through its membrane, interprets it, and responds.

Cells C and D don't do anything because either they're out of earshot, or they lack receptors to understand the language.

"I will not respond to Russian because I don't speak Russian," says Salic. "A cell that doesn't have the receptor for a given signal won't be able to interpret it."

Compared with the world's estimated 7,000 spoken languages, cells communicate using 20, including Notch, Jak-STAT, and Hippo. Each language has many dialects. The G protein-coupled receptor family, for example, includes a thousand different olfactory receptors, each dedicated to a specific smell.

Salic is learning to speak Hedgehog, a language crucial for stem cell differentiation and maintenance, which, if uttered too infrequently or too often, can cause birth defects or basal cell carcinoma. He builds tools that reveal in more detail how Hedgehog messages are created, sent, received, and translated into action.

Salic recently found that Hedgehog-speaking cells within the same tissue can be

variably competent in the language. He's now investigating what the biological significance of this finding might be.

Mother Tongue

Embryonic stem cells are born fluent in every language. As they differentiate, they lose receptors they don't need, thus narrowing the number of languages they can articulate. A lung cell ends up with a different combination of receptors from that of a neuron.

Spyros Artavanis-Tsakonas, an HMS professor emeritus of cell biology and the chief scientific officer at Biogen Idec in Cambridge, Massachusetts, has helped teach the world the grammar and syntax of one of those languages: Notch. He has identified many of the molecular components that allow cells to speak, hear, and act on Notch messages as they differentiate.

Lately, he's dreamed of listening to all cell conversations, the equivalent of pinning microphones on every person on Earth.

"If you know that this protein talks to that one, which then talks to that one, and so on down a line of fifty proteins," he says, "then if something goes wrong, you have not one drug target but fifty."

Semaphore

Sometimes the language of cells is expressed not in words, but in signals. Many cells receive the same molecular signal but react



in different ways. According to Flanagan, signals are more like spatial and temporal coordinates that cells use to make decisions.

"The brain and nervous system depend on a wiring diagram to function, like a computer. Except they have to wire themselves up," says Flanagan. "It's mind-boggling."

Earlier in his career, Flanagan was one of the first to identify axon guidance cues. More recently, he found that they sometimes act like Goldilocks: at low concentrations, the cues will beckon developing axons closer, but at high concentrations, will warn them away. This push-pull positions the growing axons at just the right distance from the signal-emitting cells.

Flanagan hopes his research will uncover a clue for coaxing axons to regrow in adults after brain and spinal cord injuries. Scar tissue that forms after trauma contains cells that broadcast inhibitory signals to prevent the injury from spreading. Axons hear the "keep out" message and don't regenerate in the injured tissue.

"We're trying to develop a therapy that makes them ignore the signals," says Flanagan.

Healthy cells listen to environmental cues. "The default for a cell is to die unless it receives the right signals from the outside," says Brugge. Cancer cells, however, undergo a series of communication alterations that allows them to move into places they don't belong and to proliferate when they should self-destruct.

Brugge recently discovered a sinister way environmental signals may shield breast cancer cells from chemotherapy. She developed a model that mimics the spherical structure of intraductal tumors surrounded by a matrix produced by normal cells. Treatment killed all the tumor cells except those in the outer layer.

Further studies revealed why: The surviving cancer cells touched the matrix, which whispered reassurances that they were in the right place.

"The signal from the matrix protects the cancer cells," says Brugge. "The cancer cells sense they're in their normal niche and rally a host of adaptations to withstand treatment."

Like Flanagan, Brugge is now searching for a way to disrupt communications for the sake of healing.

Loose Talk

However cells speak and make decisions, they couldn't function without a communications network.

Cells' signals may be like radio signals, directed at particular cells or broadcast to an entire region. Receptors, therefore, are less like ears than like finely tuned receivers, clustered on an antenna called the primary cilium.

Ever since scientists started studying cell anatomy, "they've been fascinated by the beauty of the cilium," says Salic. "It was an enigma. Now we know it impacts a huge number of developmental and physiological processes because so much signal transduction is concentrated there."

Cell communication infrastructure has vulnerabilities that enemies can exploit. Doctors and researchers are learning how they, too, can hack or restore this network to thwart disease.

Brugge has found that a single ovarian tumor can contain many subpopulations of cancer cells. Crosstalk among these cells allows the tumor to metastasize, implant, and cause the buildup of abdominal fluid called ascites.

"We want to figure out what the critical communication nodes are so we can hit them and collapse the ecosystem," says Brugge.

Some treatments replace a missing signal, like L-dopa does in people with Parkinson's.

Others, such as beta-blockers, disable the receiving mechanism.

"It's like I try to call you and the number is out of service," says Artavanis-Tsakonas.

Speak Up, Please

Dig deeper into cell communication and things quickly get complicated.

"Twenty-five years ago, we thought there was one signal for one receptor. Now we're finding that each signal can have multiple receptors and that each receptor can receive multiple signals," says Flanagan. "In the molecular era, it quickly became evident that signal transduction can be a bit of a nightmare."

Once inside the cell, each message undergoes a children's game of telephone, getting amplified, split, or otherwise chemically modified as it's passed along one or more branched signaling pathways until it reaches the cell nucleus or an organelle. As if mapping those conversational flow charts wasn't tricky enough, researchers must grapple with how cells listen simultaneously to multiple messages to make decisions.

"Signal integration is very important and very mysterious," says Artavanis-Tsakonas.

These days, researchers painstakingly inactivate one gene at a time in a given cell to find out what cellular components are necessary for a signal to produce a response. Even when that response is "simply" to activate a gene, the product can change depending on RNA splicing, the action of noncoding RNAs, and other factors.

"In short, it's complicated," says Brugge. "We used to just look at mutations and DNA. Now we have to look at so many other variables to understand what leads to dramatically different cellular responses."

But complexity has its advantages. Combining a limited group of signals in inventive ways allows organisms to develop a variety of biological processes—and to evolve.

That's why Hedgehog, Notch, and other languages appear again and again in different contexts in the human body, says Salic.

And when all animals use the same cellular languages, a certain degree of flexibility explains "how the heck you can build a worm, a fly, and a frog" from them, says Artavanis-Tsakonas.

All this diversity of life from 20 languages. Combining them produces nature's most beautiful literature. ■

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.



SMILING
MIGHTY
JESUS



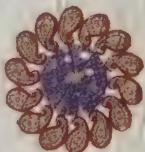
FIREBALLS



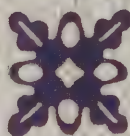
STRUTTED
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OLD
TIMER'S
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SALT
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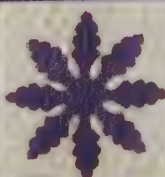


RIFTING



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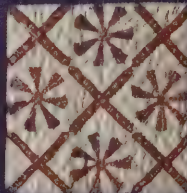
PIPJENNY



LOCKED
BOWELS



JAGS
IN MY
LEADERS





In the clinic, making oneself understood is one thing. Knowing what the patient is saying—really saying—is another by David Cameron

ON SPEAKING TERMS

Douglas Kelling '72 was born and raised in rural Missouri, which he pronounces “Missoura.” Calling it either “Missouri” or “Missoura” is a regional quirk, determined, some say, by whether you’re from the eastern or western part of that state. As regionalisms go, it’s trivial when compared with those Kelling, now an internist at the Carolinas Medical Center–Northeast in Concord, North Carolina, faced when he entered Harvard College in the mid 1960s. There he learned that water fountains were “bubblers” and that a milkshake lacked ice cream, unless it was a “frappe.” During his internship at Duke University Hospital,

Kelling discovered that, despite his Ivy League credentials, communicating was becoming more, not less, complex. One night in the emergency department a man arrived in distress. In describing his symptoms to Kelling, he added, “I’ve lost my nature.” ■ Kelling didn’t know what to say. In fact, he didn’t know what to ask. “I thought he was heading toward some kind of psychological problem,” he says. Kelling excused himself and asked a resident if he’d ever encountered that phrase before. He then learned that “losing one’s nature” was a regionalism for erectile dysfunction. ■ Words. Communication’s greatest offenders.

Doctors spend years learning how to effectively diagnose patients, a process that is equal parts art and science. In addition to reading lab reports and feeling for lumps, they also need to pick up nuances of mood, gesture, and expression. Call it the art of noticing. Medical schools understand this and often use creative ways to instill this skill in students, such as with visits to art museums where students are taught to defamiliarize themselves with what they perceive in order to see in new ways.

But what about language? Medical schools teach the arcane vocabulary of biomedicine, and yet physicians often care for patients who speak in other idioms. Simply put, different people have different words for the same things. This fact profoundly affects the patient-doctor relationship.

What's That Again?

"Losing one's nature" isn't the only new phrase Kelling has picked up. There is "smiling mighty Jesus" for spinal meningitis, or "old timer's disease" for Alzheimer's. "Fireballs" are uterine fibroids while "strutted feet" are swollen ones. "Locked bowels" call attention to constipation. "Tentacles" are, of course, testicles. There are more; many, many more.

"It's clear from our research," says Joan Hall, the chief editor of the *Dictionary of American Regional English*, or DARE, "that people still use hundreds of regional terms for ailments and diseases. Doctors are often totally unfamiliar with those terms. This unfamiliarity can make patient-doctor communication extremely difficult."

DARE began in 1965 when the American Dialect Society recruited a group of 80 field workers, dispersed them within selected communities, and had them collect regional terms, cataloging, for example, that a pan is a skillet is a spider. This historical dictionary project, always expanding, always changing, continues to this day. Its editors seek the earliest written examples for a phrase and trace the evolution of its usage.

Hall herself is a living, breathing well-spring of lexical exoticisms. She effortlessly references "pipjenny" (pimple) and "salt rheum" (eczema) and can nod sympathetically to anyone who is "rifting" (belching) or has "jags in their leaders" (sharp pains in their tendons and ligaments).

Lest you think potential misunderstandings are trivial, consider this. In 1995, one of Hall's DARE colleagues was contacted by a psychiatrist in Chicago who treated patients

She effortlessly references "pipjenny" (pimple) and "salt rheum" (eczema) and can nod sympathetically to anyone who is "rifting" (belching) or has "jags in their leaders" (sharp pains in their tendons and ligaments).

suffering from aphasia, a neurological disorder in which one loses the ability to express, or comprehend, speech. The doctor had questions about a handful of strange terms.

Aphasia is typically diagnosed using the Boston Diagnostic Aphasia Examination, a series of tests that assess basic language function. In one part of the exam, called the Boston Naming Test, patients are shown simple line drawings of common objects—such as a mask, a pair of stilts, a harmonica—and asked to name them. Responses are recorded, compared against an answer key, and the patients are scored. Simple, right?

According to Hall, the psychiatrist had examined the data and was troubled by an odd pattern: patients from the South tended to fare worse than those from the Midwest. But even responses from Midwesterners could be considered "wrong" if they were not deemed to be standard by the northeastern test-makers. Southern patients, for example, often said tommy walkers when shown a drawing of stilts, and would identify a harmonica as either a harp or a French harp. Midwesterners, on the other hand, often called the harmonica a mouth organ. After scouring old tests, the psychiatrist and his colleagues estimated that 13 percent of nearly 1,400 patients given the Boston Naming Test had been mis-scored, an outcome, says Hall, that may have subjected them unnecessarily to courses of language therapy. The physicians presented their findings at the International Neuropsychological Society in 2000.

Hall says she was pleased to note that the 2001 edition of the naming test's answer key had added a few variants, including false

face for mask, and harp and mouth organ for harmonica, as acceptable alternatives; she hopes that efforts to broaden the recognition of regional variation will continue.

"You simply can't rely on an answer key that doesn't allow for variation," says Hall. "This drives home the fact that we can't assume that our language is what everybody else speaks."

Crossword Puzzles

The multicultural makeup of the United States brings with it a diversity of verbal expression that the increasingly professionalized field of medical interpretation is helping to decipher. For the past 14 years, Dharma Cortés, an HMS clinical instructor in sociology in the Department of Psychiatry at Cambridge Health Alliance, has been training people in medical interpretation.

After receiving a doctorate in sociology, Cortés spent two years studying medical anthropology in the HMS Department of Global Health and Social Medicine. Anthropology has served her well, because medical interpretation requires more than bilingualism. The interpreter must be a cultural broker as well as someone who can translate the languages being spoken in the clinic, including the argot of biomedicine and health insurance.

"Think of the situation from the patient's perspective," Cortés says. "You go to the doctor because you sense something is wrong. During the visit you might learn something new about yourself. Something about you or your life needs to change. That triggers anxiety. On top of this, there is a language barrier that requires the presence of a complete stranger who must interpret the deeply personal information you provide to the doctor. It can become very confusing. Any misunderstanding can adversely affect the patient's follow-through when she goes home."

Cortés has witnessed firsthand the fumbling of such communication. Once, she observed a community health worker—not a trained medical interpreter—tell a patient that her blurred vision was the result of diabetic retinopathy. The worker translated, "You have diabetes in your eyes."

"So the most important thing," says Cortés, "is to render a complete and accurate interpretation, not one that includes only what the interpreter thinks is important. You can't distort, omit, embellish. For example, if the patient says, 'I have a pain that comes and



TOMATO, TOMAHTO?: Patients with aphasia who are tested for language comprehension and expression are sometimes given the Boston Naming Test, which includes an object identification section. Researchers found that nonstandard responses—such as referring to stilts as tommy walkers—could trigger unnecessary calls for courses in language therapy.

goes,' the interpreter can't abbreviate to 'I have a pain.' What seems like a small omission can have tremendous diagnostic implications."

Descriptive Elements

Sonya Shin '97, an HMS assistant professor of medicine at Brigham and Women's Hospital, practices medicine in Gallup, New Mexico, a small city that borders the Navajo Nation. Her job is to train community health workers to work with members of that nation in all areas of health and preventive medicine. Shin herself is not a tribal member, nor is she fluent in Navajo, part of the Athabaskan family of languages. Navajo, in fact, has more speakers than any indigenous language of the United States or Canada. If language is more than a mere communication medium for symbols and sounds, the Navajo tongue is truly an entire cultural landscape all its own.

Shin has worked with Spanish-speaking patients in Boston, and she has worked in Russia as well. Her observations have led her to conclude that linguistic differences seem to track with cultural ones. The larger the

divide between another language and your own, the greater the chance of all sorts of misunderstandings. Take, for example, the phrase "palliative care." You might know the precise translation, but to the Navajo, simply bringing up the subject of death is taboo. And that leads to what is perhaps the deepest difference between Navajo and almost any other language in the West: words contain a sort of residential power. By speaking something, you might be summoning that very thing.

The first thing that Shin noticed when she began working with the Navajo was how their language was far more descriptive than English. The Navajo equivalent for "cancer" can roughly be translated back into English as "a cell that comes from a healthy cell but becomes unhealthy." Much of the language is like this—indirect and descriptive of a process.

"If I'm talking with a patient," says Shin, "and I tell him that if he doesn't take his medication he might have complications with his kidneys, a Navajo person, at a cultural level, might take that to mean that I am essentially

willing it to happen. Instead, I would have to tell him how other patients I've taken care of, people who share this same condition, have found that when they don't take their medications, they have complications. You simply can't speak about prognosis in a direct way."

Nor can you look someone directly in the eye, a gesture taken as a challenge. For anyone raised in a Western society where frankness is a sign of virtuous courage, learning to become verbally and physically oblique might as well be learning another tongue.

"I have really grown to appreciate how some cultures place such power in the spoken word," says Shin.

Spellbound

Shin may have had to travel across the country before experiencing cultural vertigo, but sometimes it comes to you.

In his early days as an intern at Duke, Kelling had gotten to know a young Haitian man who repeatedly showed up in the emergency department, each time with vague symptoms. He was nervous, anxious, depressed, losing weight. He couldn't sleep, couldn't eat. Kelling and his fellow physicians had no idea what was wrong.

Then, one night, the patient's mother came in with him. She pulled Kelling aside and said, "He's sick because a witch doctor put a hex on him. We need to get another witch doctor to take the hex off."

Kelling told her he didn't know of any local witch doctors, to which the mother replied, "I do," and gave him a phone number.

Kelling shrugged, but with nothing to lose, he called the number and arranged for the alleged healer to visit the emergency room.

"That's really the only time in my professional life that I've had to call a consultation with a witch doctor," he says.

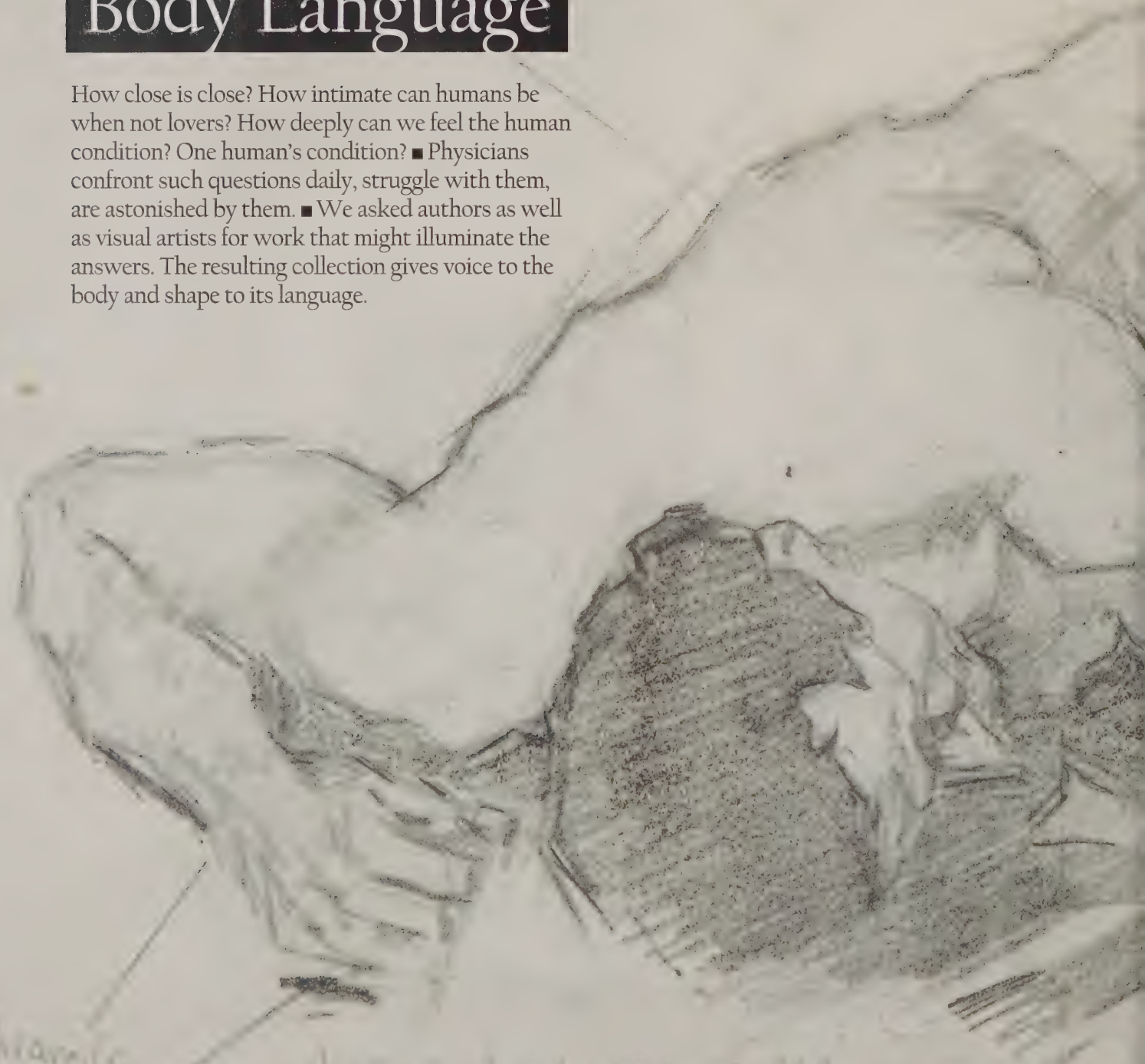
Soon the man arrived, a surprisingly unassuming person who, Kelling says, you wouldn't consider twice if you passed him in public. The witch doctor spent a few moments alone with the young man in the examination room, and, when he emerged, he simply said, "It's taken care of." He left, and the young man was fine. The weight of the world had been lifted from him.

No one knew what had transpired, and to this day, it remains an unspoken secret. To the doctors, "it" remains untranslated. ■

David Cameron is the director of science communications in the HMS Office of Communications and External Relations.

Body Language

How close is close? How intimate can humans be when not lovers? How deeply can we feel the human condition? One human's condition? ■ Physicians confront such questions daily, struggle with them, are astonished by them. ■ We asked authors as well as visual artists for work that might illuminate the answers. The resulting collection gives voice to the body and shape to its language.



Triangle
of the

Analysis of a painting by Velázquez
in which the artist's 500th birth
anniversary is commemorated. 500th



Denman Waldo Ross
*Nude Youth Lying
on the Floor, after
Velazquez, 1926*
Graphite on off-white
wove paper
25.6 x 35.7 cm





▲ Alexander Kavensky
K.B. with Kimono
Oil on wood
24 x 24 in

KATIE

Some 45 years ago, when I began my residency in internal medicine, we had a mandatory six-week rotation on inpatient psychiatry. I attended endless patient-care conferences, drank a lot of coffee, and was assigned one patient to follow during the block. My patient was Katie, a 17-year-old schizophrenic girl in the locked ward, who, responding to the voices she heard, repeatedly cut herself, slashing her wrists and forearms despite the best efforts of nursing to deprive her of any means for doing so.

Twice a day I'd see her. I'd sit and talk with her, tell her about my young son and how he loved to have me take him fishing, ask about her interests and her hopes, and, mostly, consume each two-hour visit with a very one-sided conversation. I remember feeling that,

at times, maybe we were getting somewhere, that she was improving. Then I'd find her in a tangle of bed sheets, covered in blood.

When the rotation ended and I left the psych ward for my remaining years of training, I would sometimes stop by to see Katie, who was still in the locked ward, still withdrawn, and, occasionally, still talking back to that voice in the far corner of the room. Later, during my fellowship at the same institution, she presented me with a pair of red mittens she had knitted for my son, handing them to me with her head down, avoiding eye contact, perhaps a little embarrassed by what she may have felt was a modest gift.

The years passed, filled with the occasions all doctors experience: the excitement of medicine and of the successes in treating disease, the increasing frustrations with bureaucracy and uncaring administrators, and, in the twilight of a career, the recurring wonder of whether you had really made a difference, had ever reached those increasingly disengaged students, had mattered in any way, to anyone.

Recently, on my way to meet students for rounds, I stopped to pick up my hospital mail. In the pile, I found a greeting card. I opened it and pulled the card free. It was illustrated with a pencil drawing of a little boy holding up a fish.

There was a note inside. It was from Katie.

Dear Dr. Flynn,

You won't remember me, but many years ago when you were starting your training, you took care of me. I want you to know I am fine now. I've had a few bumps in the road—a rape, eye problems

from Mellaril—but I am married now to a wonderful man, for 31 years. I went to school, got my nursing degree, and work for a doctor who is like I remember you. It's all because of your caring. That's what got me through. I found this card a long time ago and saved it. It reminded me of how you told me about taking your son fishing.

I think we should tell people who are important to us that they made a difference. So I am telling you. Thank God for you, Dr. Flynn. I hope you will remember me.

Yours truly,
Katie

As I was reading, I had sunk against the mailroom wall. Tears streamed down my cheeks. A passing housekeeper stopped and asked me if I was okay.

"Yes," I said. "Yes. I am very okay."

The author, a graduate of HMS, practices internal medicine. All names associated with this story have been changed or withheld to ensure the patient's privacy.

◀ Ron Cheek
Woman with a Burden
Oil on canvas
68 x 40 in



MAGNIFY AND SIMPLIFY

"I sit in the library," a patient once said of his long days, "and try to force a daydream." About his own illness, he said, "it's like a patch over one eye. Or like being in a submarine: you can't see what's above the water if you don't lift the parasite. But of course," he added, "it's also a free sky."

He was speaking English, but also another language, not just the language of schizophrenia, in which he is fluent: It was more like the language of haiku.

We should learn it.

Words, condensed and brilliantly chosen, could clarify a lot of common obscurities. In its guidelines, the Haiku

Society of America describes the poetic qualities of *wabi sabi*: *wabi*, "unpretentious suchness of the ordinary," and *sabi*, "a sense of hopeful sadness or recognition that nothing lasts, nothing is perfect, nothing is finished." Oh no, you think, another fancy existential round-you-go. But the point is not to speak existentially. It is to speak essentially.

We use words constantly, frantically, hopefully, desperately, and yet, generically, without taking the time to notice what we are saying. Would the world change if we each spoke a variant of haiku? If not (and we might argue here), would it at least change if we listened?

Putting things idiosyncratically—outside of their pro forma descriptions, the kind you can hear while doing other things—is poetry, prayer, pillow talk. Or it's standard fare. For instance, apparently the Zulu translation for the English phrase "far away" is, "Where one cries, Mother, I am lost." It strikes the heart down to hear. Then there is a Fuegian seven-syllable word that in English translates to: "they look at each other, each waiting for the other to offer to do that which both desire but neither wishes to do." This is the opposite of being struck dumb. This is being struck into understanding.

Words used this way tell us what we know but hadn't known we knew. They give the truth a shape you feel compelled to share. You want to turn to the stranger next to you and marvel: "Mother, I am lost." It wouldn't be so bad to speak outside the vernacular in order to share more truth.

The other day I saw my schizophrenic poet again. I was wobbling on high heels, looking most unlike the person he usually meets. He had a hard time recognizing me. It was an experimental identity: I didn't really recognize myself.

He looked down and, being a polite man, tried to refrain from judgement. But he couldn't help his commentary. "Kung fu?" he asked at last.

Good Lord, I thought, nearly stumbling from comprehension. Could he have said it any better?

—Elissa Ely '87

Ely is a psychiatrist at the Massachusetts Mental Health Center.

◀ Alejandro DeCinti
Contraluz, 2008
Oil and alkyd on canvas
55 x 46 cm

▼ Willow Bader
After the Dance, 2010
Encaustic
12 x 12 in







▲ Antoine de Villiers
Yield Strength
Pencil on paper
41 x 51 cm
(from 81 x 51 cm diptych)

◀ Colleen Barry
Academic Male Nude, 2011
Oil on linen
25 x 25 in

THANKS

What can we learn from the dying beyond a sudden sense of our own mortality? Is there anything to be gained beyond the poignancy of the moment?

Does it matter?

A husband comes to the hospital to visit his sick wife. She asks the doctor to have a look at him as well. There he stands, a woodsman of enviable strength, unnerved by the pristine antisepsis of the hospital. Behind him, apart and withdrawn, stands their mentally disabled son, in his midthirties, lurking by the drapes with feral eyes. He peers at the doctor as though from some dark cave, face expressionless, filling the doctor with an uncommon fear.

What begins for the woodsman as fever and troublesome speech ends two weeks later with coma, flaccid paralysis, agonal breathing, and death. During those intervening weeks, the doctor treats him with rare intensity, applying esoteric medication, calling in the brightest consultants, fine-tuning the delicate machinery of intensive care. The man's wife and daughters hover at the bedside through it all, shocked at the suddenness of his devastation, at this reversal of fortune. She had been the sickly one; now he is at Death's dreadful door.

Through all of the doctor's frantic attention to his father—the urgent summonses to the bedside; the late, sleepless nights before the monitors; the spinal taps and respirator care—the man's son stands against the wall and watches, silent. Never altering his stonelike expression, his eyes shift to the nurse, running off with an order; to the doctor's hands, probing for hope from his father's body; to his mother, weeping; and to his sisters, unable to manage their

anger and despair. At the end, he watches the monitor go straight-line, watches a finger flick off the respirator, sees the slow, sorrowful nod to his mother. The physician leaves the family there with the deceased, and, with the nurse, walks into the hall, exhausted. There they stand, nurse and doctor, saying nothing, each staring off at some point far away.

Then the doctor feels something at his arm. He turns to find the son standing beside him, eyes dark and sad. He has touched the doctor's arm with the point of his index finger.

"Thanks," he says, and walks away.

The nurse, who has been hardened by the swirling decay of society that manifests in metropolitan hospitals, is overcome.

"Oh Christ!" she says, and buries her face in her hands. The doctor, fighting to control his own emotions, holds her tightly and walks her down the hall.

—Michael LaCombe '68

LaCombe is a cardiologist at the MaineGeneral Medical Center in Augusta. For the past 23 years, LaCombe has served as editor of the "On Being a Doctor" and "Ad Libitum" sections of the Annals of Internal Medicine. His twelfth book, Bedside: The Art of Medicine, was published in 2010 by the University of Maine Press.



Truls Espedal
The Circle
Oil on canvas
70 x 50 cm

THE STETHOSCOPE REPLIES

I've heard this one so many times before:
 the story of some awful heartbreak, or
 the murmuring of love found at long last.
 A breath is held, while silently the pain
 returns; the scratching of the tiny crab
 too many years of smoking left behind.
 I've heard it all before, the agony
 of drowning in the flood of one's own blood
 that slowly rises from some inner wound;
 the barking cough that proves we're animal.
 They press me to your chest, so I can hear
 it all, the song of the alveoli
 end-expiratory, musical wheeze,
 the sinister, if not ironic rub.
 I've heard it countless times before.
 Even the sound of sobbing, so plain
 it surely doesn't need my amplifying,
 though still you try to speak, even when the tube
 (I know by checking breath sounds afterwards)
 is placed. I've heard it all before, the ebb
 and flow of life, the pure monotony
 of wanting somehow to express the wish,
 the need to live. I touch you silently,
 and listen, nestled in your wrinkled breasts,
 or at the angle of your jaw, so cold
 in my unspeakable amazement.
 Inhale, exhale. I've heard it all before.

—Rafael Campo '91

Campo is an HMS associate professor of medicine at Beth Israel Deaconess Medical Center. In 2013, he won the Hippocrates Prize for Poetry and Medicine, a prestigious international poetry prize that recognizes unpublished poems that address medical topics, for his poem "Morbidity and Mortality Rounds." Campo's sixth collection of poetry, *Alternative Medicine*, was recently released by Duke University Press.

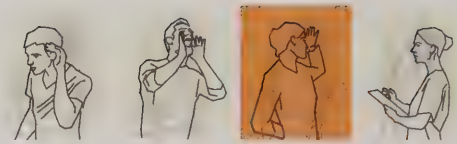
Laura Ferguson
*Bronchial Tree (gold
 mezzo version)*
 Oils, bronze powder,
 charcoal, and pastel pencil
 on paper
 9.75 x 8 in



A zebra finch is shown in mid-flight against a plain white background. The bird's wings are spread wide, revealing the intricate patterns of its feathers. It has a grey head with a black stripe through the eye, a bright red beak, and a red patch on its cheek. Its body is covered in a mix of brown, white, and black spots and stripes. The bird's legs are extended downwards.

Field N

A fascination with baby babble leads a pediatrician



otes

to birdsong by Perri Klass

At well-baby visits, when it's too early to ask about spoken words, I always ask about babble. ■ You want to hear that a four-month-old is producing babbling noises, heavily oriented toward vowel sounds. You hope that by around seven months, the baby is progressing to "canonical babbling," which involves the production of what sounds like syllables, complete with consonants: *ba, da, ma*. ■ Why worry about a baby who doesn't babble? >>





She may be signaling that there's something getting in the way of speech development—a hearing problem or a general developmental delay. And to parse a baby's silence, you would surely ask the medical students or the residents, “If the baby's hearing is perfect, and the baby's development seems absolutely normal, what should be your next concern about this baby who isn't babbling?”

You would pause, hoping someone says, “Is anybody talking to her?”

You then would review how much goes into those deceptively simple baby noises—sensory, motor, cognitive, social—and how many things can go wrong.

A couple of years ago, thinking about these exam room interactions, I reviewed some of the scientific literature on human baby babble, a topic that has attracted researchers interested in speech and hearing as well as those interested in learning and the brain. Babies must learn to talk; their bodies and brains are, in fact, designed to learn this skill. Speech acquisition is a miracle of interlocking systems, ranging from the muscle control and laryngeal gymnastics involved in producing immature sounds, to the iterative process of refining those sounds into recognizable words, to the cognitive work of arranging

those words into sentences and weaving those utterances into social interactions and relationships. If something goes wrong—in oral-motor muscles' coordination or development, in acoustic and auditory processing, in cognition and memory formation, or in social stimulation—speech and language may be absent or delayed, putting the child at risk of isolation from the give and take needed to be a member of a family, a part of a culture, and ultimately, an engaged citizen of society and the world.

To further explore the science of babble, I spoke to experts who study speech and hearing, and learned about experiments that attempt to sort out how babies use their muscles to create sounds, and how they then practice repetition to bring those sounds closer to speech. Other researchers described the ways babies mimic the sounds they hear and mentioned the importance of the deliberate, exaggerated speech that has been called “motherese,” or “parentese.” Neuroscientists looking at speech see the connections between auditory and motor areas in the human brain, and study how babies learn by trial and error the oral-motor differences between producing specific meaningful sounds.

All of this made sense; these avenues of inquiry converged again on those exam room

questions and concerns over sensory, motor, cognitive, and social development. But what I hadn't expected was that so many of those roads also led to birdsong. Or that birdsong would present so many answers, and new questions.

Voice Lessons

Many animals make sounds of a predetermined, characteristic nature no matter how they are raised—even if raised in isolation or with a different species. They are, in short, wired for their sounds. Babies and many songbirds, by comparison, have the muscular hardware and the neural software for making sounds, but the specific speech and song they produce are heavily dependent on learning.

Like humans, songbirds have critical developmental periods during which they are able to learn to reproduce the sounds made by those around them. Cross-fostering experiments have shown that many types of birds raised in a different family or species can reproduce, with some constraints, the songs they hear, not the songs of their biological origins. And of course, it doesn't matter where a human baby is born, or what language that baby's biological parents speak; the baby will learn to speak the language he grows up hearing.

Researchers have long been fascinated by the parallels between the imperfect, immature songs of young birds and the early attempts at speech made by human babies.

“From the perspective of human speech development, the early stages of learning are the most interesting, when both birds and humans go through a stage of babbling, uttering highly variable vocalizations,” says Bence Ölveczky, the John L. Loeb Associate Professor of the Natural Sciences at Harvard University. Ölveczky studies motor learning in animals, including song production by birds. He is particularly interested in the basal ganglia, which play an important role in the bird's ability to go from vocal experimenting, the equivalent of babble, to producing mature song.

For those experiments, Ölveczky studies zebra finches, songbirds most often found in

Researchers have long been fascinated by the parallels between the imperfect, immature songs of young birds and the early attempts at speech made by human babies.

Matsumura Keibun
Zebra Finch and Cherokee Rose
Late Meiji, October 1892
Japanese woodblock print,
chuban format
21.5 x 27 cm

景文花鳥畫譜後篇之十



Australia. Although smaller than your closed fist, these birds are loud and lusty singers, even in captivity. Or at least the males are. As with many songbird species, the males sing, learning their songs from their fathers, but the females do not.

Ölveczky calls zebra finches “expert animals,” pointing out that their brains are specialized for learning the complex song sequences they produce. “We can learn a lot from expert animals,” he says. “They have evolved dedicated neural circuitry optimized for a particular task. As mammals, for example, we are more generalist animals, our brains are less differentiated, we’re sort of half good at a lot of things. Birds have much more differentiated brains. They’re experts.”

Takao Hensch, an HMS professor of neurology, studies the mechanisms of critical periods of brain development, the windows of time when the brain is particularly sensitive to experience. His laboratory is looking at mice to see what turns these critical periods on and off.

According to Hensch, much important information on critical periods has come from birds. The song of the zebra finch, once learned, is crystallized for life. “Other birds, like canaries, are seasonal singers and repeat this process annually,” he says. “That’s how neurogenesis in the brain was discovered—certain songbirds reopen the critical period, and they actually have a rebirth of neurons.”

Allison Doupe ’79, a professor of psychiatry at the University of California, San Francisco, has also studied the cortical basal ganglia pathway in zebra finches. Her research team has focused on this particular part of the brain because in birds, as in humans, the basal ganglia are essential for learning and controlling movements—including the complex set of movements needed to produce a characteristic mature song.

“We study songbirds because they are vocal learners and because they have brain areas specialized for producing the song and for learning the song,” says Mimi Kao, a

postdoctoral fellow at UCSF who is part of Doupe’s research team. “If you have a juvenile bird with a damaged circuit, the bird will never produce a good copy of the song.”

Doupe and her colleagues have looked at the neuronal detail of the pathway—recording the activity in the brain while the bird is singing and then examining the patterns of neuron firing—and have demonstrated that these patterns are highly sensitive to social context and to the stimulation that the bird receives.

“When males are singing by themselves, the brain activity varies from one song to the next,” says Kao. “When a male sings to a female and he’s singing the same song, the activity looks much more stereotyped and precise.”

Or, as Doupe and Patricia Kuhl, a professor in the Department of Speech and Hearing Sciences at the University of Washington, Seattle, put it in a landmark article published in the *Annual Review of Neuroscience* in 1999, “the social factors required by zebra finches can come in a variety of modalities, all of



which may serve to open some attentional or arousal gate, which then permits sensory learning.” They went on to write, “Infants engaged in social interaction appear to be highly aroused and attentive, which may play a role in their ability to react to and learn socially significant stimuli.”

Duets

So, babble matters, and birdsong is important for thinking about babble—as model, as mechanism, even as metaphor. People who study baby babble and those who study birdsong are aware of the neurological parallels. There are “baby researchers” who cite birdsong, and “bird researchers” who cite babble.

I talked with Michael Goldstein, who cites, and studies, both.

Goldstein is an associate professor of psychology at Cornell University. In a building on that campus, he and Jennifer Schwade, a research associate, run the Behavioral Analysis of Beginning Years lab. Yes, the B.A.B.Y. lab. Upstairs, they study human infants, and adults; downstairs they study young and mature zebra finches. I spent a couple of days in that building, moving from floor to floor, watching the researchers study the babies and listening to the songs of the finches.

In the upstairs lab, the researchers conduct baby-parent studies, looking at the ways that babies elicit speech from their parents and how the social context of this kind of back and forth affects the baby’s skill as a learner of speech and language. Downstairs, they study zebra finches, concentrating on how social interactions shape the vocal learning that produces the song.

Thus, two very strong strands of inquiry twist together: the people who look at what is called song production in the birds are the same people who look at how human babies

So, babble matters, and birdsong is important for thinking about babble—as model, as mechanism, even as metaphor.

learn to master and interpret the language of the world around them.

Much of what the researchers study in the human babies concerns the effect that the mother’s responses have on the baby’s vocalizations and on vocal learning. “The caregiver reacts,” says Goldstein, “and the infant modifies the sounds. As the sounds become more speechlike, the caregiver is more likely to react. So babbling has a crucially important function, but you’re only going to see it if you study babbling in a social context.”

It turns out it’s also best to study the birds in a social context. Goldstein’s team studies the ways that adult birds, both males and females, react to immature birdsong, and the ways that those reactions shape a young bird’s learning. This involves studying not only the song that a father, or other adult male, may produce, but also the behaviors,

such as wing movements and so-called fluff-ups, that convey a response from a mother or other avian female. Upstairs and downstairs, development is studied as part of a social system, in which a young learner’s immature utterances elicit responses that then help the vocalizations develop and mature.

Score Marking

All of the researchers I contacted are people who love to think about the whys and wherefores of human speech. Talking with them or reading their research takes you from brain structure and function to learning and memory, and from statistical learning—the neurological mathematics of frequency, the process by which babies’ brains figure out parts of speech and syntax—to how simple mechanisms, such as parental responses to a baby’s sounds, can help generate complex communications.

While at Cornell, I listened carefully to the songs of the zebra finches as the researchers pointed out the immature, plastic song of young birds and the mature song of the adults, song that has been shaped by stimulation and social interaction. Now, in the clinic, I again listen carefully—and, perhaps, with added awe—to babies as they babble their way toward language and communication. ■

Perri Klass '86 is a professor of journalism and pediatrics and director of the Arthur L. Carter Journalism Institute at New York University.





The written word can be the
most personalized medicine

by Ellen Barlow

By carefully listening to “half-spoken words,” William Carlos Williams found poetry in the relationship between doctor and patient. He wrote in his *Autobiography* that his two occupations—acclaimed poet and rural family physician—stimulated and supported one another, “that they are two parts to the whole, that it is not two jobs at all, that one rests the man when the other fatigues him.” ■ Today, doctors—and medical students—are telling their stories everywhere, in blogs, books, magazines, newspapers, and in personal reflections in professional journals. Cultivating creativity, reflection, and compassion, say those who are involved, enriches the lives of doctors and doctors in training and enhances their care of patients. ■ Patients are also finding that writing about their illnesses gives them a voice and helps them make sense of their experience. Numerous studies in the psychiatric literature show that writing about one’s feelings or experiences positively affects emotional and physical health. Writing helps people realize that although they might not be able to change their diagnosis, they can control their attitude toward it. ■ Writing, it turns out, is a prescription that equally serves patient and physician.

*script
writing*



WORDS OF COMFORT: By turning to the written word, Anne Brewster (from left), Peter Selwyn, Lisa Gruenberg, and Susan Pories have helped themselves and other physicians work through the complicated emotions that attend their profession.

Taking Notes

Physicians, like anyone else, start writing for a variety of reasons.

Peter Selwyn '81 was prompted to write to help himself make sense of the early years of the AIDS epidemic, when a diagnosis of infection with HIV was a death sentence. He graduated from HMS the same week that the Centers for Disease Control and Prevention reported the nation's first cases of what would come to be described as AIDS. Later, as medical director of the drug abuse treatment program at Montefiore Medical Center in the Bronx, Selwyn was on the front lines of the epidemic. There, he says, he became a witness to "desperation and suffering, but also to courage and solidarity."

By caring for dying patients during that first decade of the AIDS crisis, Selwyn was able to confront and come to terms with his own personal losses, primarily the death of his father to apparent suicide when Selwyn was only 18 months old. The shame he experienced after finding out the truth about his father's death was, he felt, akin to the shame his AIDS patients were experiencing. "It was a period of incredible challenges and transformation, and I wanted to preserve that in a memoir," says Selwyn. That memoir, *Surviving the Fall: The Personal Journey of an AIDS Doctor*, became a nominee for the National Book Award.

In 2008, at Montefiore, Selwyn and his colleague Paul Gross started *Pulse: Voices from the Heart of Medicine*, a weekly electronic newsletter and website that offer patients, physicians, and medical students, including students from Selwyn's family medicine clerkship, a place to post personal stories,

poems, and pictures. *Pulse* explores the physician-patient relationship from all perspectives, often showing the deep human connection that is so characteristic of caregiving and receiving. The website draws a worldwide audience, and, to date, Selwyn and his colleagues have fashioned two anthologies from the postings.

Developing the skills for dealing with unresolved grief or loss is essential for physicians in training and those in practice, says Selwyn, now professor and unified chair of the Department of Family and Social Medicine at Montefiore and Albert Einstein College of Medicine. "Once I became aware that I had never come to terms with the loss of my father," he wrote in his memoir, "I began the work of grieving both for my father, which I had never done, and for all of my patients who had died. After going through this process, I found that I had become better able to be with my patients in their pain."

For Lisa Gruenberg, an HMS assistant professor of obstetrics, gynecology, and reproductive biology at Brigham and Women's Hospital, writing has made her better at recognizing suffering—and at listening. "Arts and particularly writing are tremendously clarifying," says Gruenberg. "A lot of times what people tell you is not the same as what they are worrying about. As a clinician, I must identify and address those worries."

In addition to seeing pediatric and adolescent patients on a part-time basis in the Gynecology Division at Boston Children's Hospital, Gruenberg writes at The Writers' Room of Boston; is involved with teaching

HMS students the anatomy and histology course, Human Body; and serves as a member of the International Medical Surgical Disaster Response Team/East, based at Massachusetts General Hospital. She has published several essays, and her book-length memoir, *Searching for Mia*, is being considered for publication.

Gruenberg started writing in 2004 during a time of personal upheaval. Her father, who lost most of his family during the Holocaust, was having flashbacks to painful times he experienced as a teen in Vienna during the Nazi occupation. In her writing, Gruenberg channeled what she felt were the words of her father's sister, Mia, who disappeared in Germany in 1941, when she was 15 years old. "I found the writing incredibly painful," she says, "and stopped after four or five months."

Although writing about her father and her search for his sister was not cathartic for her, Gruenberg says, she nonetheless resumed the project. She maintains that rewriting and making sentences sing is a joyful process.

Now she runs writing workshops that aim to help HMS students and others to freely express themselves. "I think it is easy to lose your altruism when you're busy," she says. "Writing allows us to reflect; I think it helps us preserve that altruism."

Story Hour

Anne Brewster '99 found writing to be empowering, both as a doctor and as a patient. After learning she had multiple sclerosis, Brewster, an HMS instructor in medicine, spent years refusing to accept the diagnosis, in part because she was ashamed.



The first time she spoke about it to anyone outside of those in her closest circle it was to a patient, frightened by receiving her own diagnosis of MS. Brewster realized that such personal sharing was atypical and not always appropriate, but in this case her intuition told her it was the right thing to do. “Being a doctor in that moment and realizing that my opening up helped my patient freed me to write about my disease,” Brewster recalls. “Writing brings both vulnerability and empowerment. It’s giving voice and facing that vulnerability, which ultimately gives you strength.”

Brewster has written for radio and newspaper blogs as well as for print newspapers. Struck by how personally therapeutic sharing her story had been for her, Brewster decided to help patients tell theirs. She now produces audio stories for an NPR station’s health blog and recently launched a nonprofit, the Health Story Collaborative, which publishes patient stories online and hosts live storytelling events.

Brewster feels it’s crucial to keep the patient voice alive in health care. She thinks that the 15-minute appointment that characterizes medicine today offers little to no time to ask patients about their lives and closely listen to them. “This is a huge part of healing that I think we’re in danger of losing,” she says. Concerned and disillusioned by the inability to give patients the time she believes they require, Brewster left primary care in 2008 and is now an urgent care physician at Mass General, where, paradoxically, she has found more time to connect with patients.

Brewster is working on an idea for story-sharing events that would allow patients and medical students or providers a means for learning each other’s perspective. “We are on the same team, but I think both doctors and patients are unhappy and yearn for more authentic connections.”

Charting Experiences

At HMS, writing has been part of the curriculum since the late 1980s. One course, Patient-Doctor III, requires students to write about their experiences when they first go on the wards. According to Susan Pories, who taught the course for 10 years, those written experiences run the gamut from what it is like to cry in front of a patient, to the helpless feeling that strikes when facing someone with massive burns, to the questions that follow the death of a child: was the mother effectively involved in the process, was the news of the death delivered compassionately enough. Pories, an HMS associate professor of surgery and medical director of Mount Auburn Hospital’s Hoffman Breast Center, together with colleagues Sachin Jain ’06 and Gordon Harper, published one collection of student essays called *The Soul of a Doctor: Harvard Medical Students Face Life and Death*.

To provide a forum for medical students who are interested in writing beyond their classes, Pories started an evening writing group about a decade ago. Each year between 5 and 10 students participate in the group. Many of the students have already had their work published. This year, Pories co-led the evening sessions with

poet-physician Rafael Campo ’91, an HMS associate professor of medicine at Beth Israel Deaconess Medical Center. Among their guests were former U.S. poet laureate Natasha Trethewey and essayist Danielle Ofri, a physician at Bellevue Hospital in New York City.

The depth of interest that Pories finds among the students and faculty she works with seems to be mirrored in the wider HMS community. A recent survey of 13,512 members of the School’s community, conducted by the Committee for Arts&Humanities@HMS, a group Pories co-chairs, found that 71 percent of the respondents actively participate in the arts, and that more than half felt that medical education and patient care could be enhanced by incorporating the arts.

Such responses resonate with Pories. She remembers well a presentation during her fellowship at Mount Auburn by Rita Charon ’78, founder of the narrative medicine program at the College of Physicians and Surgeons at Columbia. Charon asked the audience to consider the Franz Kafka novella *Metamorphosis* from a different perspective. What if, she said, rather than imagining the fantastical idea that you’ve turned into a cockroach, imagine you’ve had a stroke and are paralyzed. You are not the person you were before, and everyone treats you differently.

“That’s an image that makes you think,” says Pories. “That’s the kind of thing you can do with literature.” ■

Ellen Barlow is a freelance writer based in Massachusetts.





Tool Kit

A physician reflects on lessons learned from life—and from her granny
by Tamara Fountain

Not too long ago, I removed a twig that had been festering for two months deep in the eye socket of a three-year-old boy, impaled there after he ran into a bush while sled-ding. I reassembled the fragments on the Mayo stand and instructed my scrub nurse to take a picture. Before she snapped the shot, I placed a ruler next to the twig because without it, without some standard, there was no way to gauge the size of the object (it was four centimeters, by the way). What the picture needed was perspective.



I also

needed a dose of perspective 25 years ago. My classmates and I were all cramming for Step 1 of our Boards—camped out at Countway, squirreled away in Vanderbilt Hall, making late-night falafel runs—all the while trying not to let the sight of everyone else doing the same things send us into a death spiral of insecurity, self-doubt, and misery.

The pass rate for the exam was around 95 percent. I had convinced myself that I was going to end up in that other 5 percent. I recall talking on the phone with my grandmother as the exam approached. Granny had little formal education, was married at 15, was a mom at 16, and had lived her entire life within a three-mile radius of her birthplace on the outskirts of an Appalachian Virginia

factory town. I complained to her how hard it was to study for this exam, how difficult the questions would be, how I had heard of HMS students far more intelligent than I who had flunked the test. She asked, “Well, baby, what happens if you fail?” Hearing her articulate what I’d tried to push to the back of my mind, I choked up and in a low wail cried, “Oh god, Granny, I’d have to take the test *again!*” There was a pause and her tone, until now empathetic, changed. She chastened me, in the sweet and gentle way only a grandmother can, “You mean they *let* you take the test again? You can still go on to be a doctor? Well, what are you worried about?” And she was right. I might fail the test, but with some remediation, I would not fail in

my quest to become a doctor. My Ivy League education was no match for the school of hard knocks degree my granny held.

By the way, my patients might be relieved to know that, in the end, I was not part of that 5 percent after all.

Leaning In

The ability to bounce back from, take your pick: rejection, failure, disgrace, or any of life’s many obstacles, is something that is difficult to teach and even more painful to learn. By definition, most HMS students are not initially well versed in failure and rejection; such a track record would be a certain deal breaker for the admissions committee. But by midcareer, few of us have escaped the inevitable setbacks, sucker punches to the gut, and curve balls that life seems to throw as the years tick by.

After HMS I did an ophthalmology residency. By the end of it, I was married and a mom, and had decided to pursue a fellowship in ophthalmic plastic and reconstructive surgery. I blithely hit the interview trail seven months pregnant with my second child. I had seven interviews across the country with seven fellowship directors, all men whom I expected to look past my in-your-face fecundity and conclude, “Yes, for two years, we want you to handle the resident teaching, after-hours call, and attendant scut work—on top of managing two toddlers while your husband is halfway across the country.” One preceptor, apparently reading from the handbook of questions prohibited during a job interview, inquired, “Did you plan these pregnancies?” and followed with, “And what does your husband think about your doing a fellowship?” Despite these encounters, I felt, rather naively in retrospect, that I’d impressed them as a qualified and competitive candidate. I actually had the nerve to be surprised when I didn’t match.

I finished residency and found myself unemployed with no backup plan. My

I did manage to become expertly skilled in body fluid management, in pediatric conflict resolution, and in belting out the mind-numbing cadence of the *Barney and Friends*’ theme song.

husband’s job moved us to Chicago. One year of full-time mommyhood turned into two. As my clinical skills and professional confidence deteriorated, I did manage to become expertly skilled in body fluid management, in pediatric conflict resolution, and in belting out the mind-numbing cadence of the *Barney and Friends*’ theme song.

On one raw, gray Chicago day, with the kids down for a nap, I went through the mail. My copy of *Ophthalmology* had arrived. Flipping through it, I came across an article written by one of my coresidents. Here was my classmate, stamping out blindness and building his academic CV, while the only thing I was getting good at was folding a double-wide stroller one-handed with an infant on one hip. (And I was *really* good at it.)

I’m not sure why—sleep deprivation likely played a role—but when I saw that article, I crumpled to the floor, my chest heaving with sobs. I lay there in a fetal position for a few minutes, tears running sideways across the bridge of my nose. As my breathing quieted, I realized two things. First, my son’s long-lost binky was under the sofa next to a desiccated Cheerio and a dust bunny. The second thing

was this: So what if I didn’t match on that fellowship on the first try? So what if I hadn’t seen a patient or held a surgical instrument in two years? I picked myself up off the floor and resolved to get my professional life back on track.

And I did. I landed a fellowship, in Los Angeles no less, the epicenter of facial plastic surgery. Three years later I returned to Chicago and belatedly began a career that has given me more joy than I ever thought possible. My path wasn’t a conventional one, but it still got me where I wanted to go.

That was 20 years ago. Every now and again, a particularly observant hospital credentialer will question me about the two-year gap in my work history. The first time I fielded that question, I was self-conscious, embarrassed, and a little ashamed. When I confided that I’d spent that time taking care of my kids, the perky woman on the other end of the call laughed cheerfully and chirped, “That is so cool! We just have to make sure you weren’t incarcerated or institutionalized.” As I hung up the phone, I concluded that she didn’t have kids, otherwise she’d know that early parenthood feels, on many days, a lot like both.

Little Somethings

It’s hard, though not impossible, to really know what to be grateful for when you’re young; it takes experience to appreciate how bad things can get. Substance abuse, divorce, mental illness, financial trouble, a dying parent, or worse, a dying child—we all know someone who has dealt with at least one of these issues. In medicine, we have a front-row seat for some of the worst that life dishes out.

Some of my greatest lessons in gratitude have come from my patients. Sometimes it’s been homemade Polish *paczki* around Easter or a slab of ribs from a South Side soul-food caterer. Another time, it was \$400 from a high-powered attorney, slipped into my coat pocket along with a note apologizing for how little the insurance company had paid me for his surgery.

But more often it hasn’t been a gift, it’s been the thought behind a gift: a heartfelt handshake, tears of relief and appreciation, an unsolicited hug. These gestures of gratitude are powerfully motivating and reminders of what is really important.

Points of Contact

I think each generation of doctors worries about the next. It’s natural to fear that the “good days” of medicine are over for those who follow us. So much has changed in the way health care is delivered and paid for that a doctor from the Ben Casey era would barely recognize the way medicine is practiced today.

But there are things that won’t change. As we all eat and breathe, we recognize there will come a day when we no longer will do either. During this universal journey to the end of life, almost everyone, be she rich and powerful, or he meek and disenfranchised, will turn to us, the medical profession, in that greatest hour of emotional and physical need. Technology may make us better clinicians, but there can be no app for the compassion that patients crave.

The privilege and honor that physicians have, the laying on of hands—this will not change. Who else can touch a patient in places perhaps only a lover has touched? Who else can ask a question that would be unspeakable in any other setting? Who else can literally hold a person’s heart in their hand? Lawyers don’t get to do that. Investment bankers don’t get to do that. Other professionals—news anchors, actresses, supermodels, athletes—they don’t get to do that. But we doctors do. ■

Tamara Fountain ’88, an ophthalmologist, is a professor in the Department of Ophthalmology at Rush University Medical Center in Chicago and a principal in Ophthalmology Partners, Ltd., in Deerfield, Illinois. This article is adapted from her presentation at her HMS class’s 25th reunion in May 2013.

BACKSTORY

FROM THE COLLECTIONS AT HARVARD MEDICAL SCHOOL

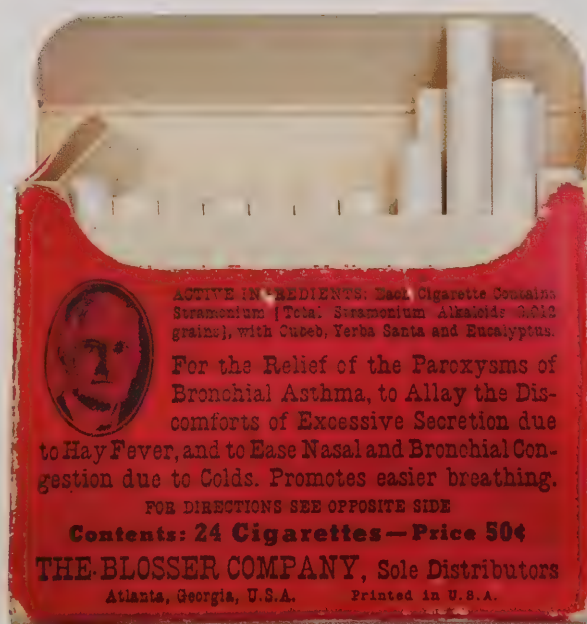
Since before recorded history, elixirs and wonder drugs have been marketed to the unwary, the gullible, and, most tragically, those in great suffering. The past century, however, has witnessed efforts to establish the safety of such nostrums.

Beginning in 1906 with the Pure Food and Drug Act, the story of food and drug regulation in the United States has been one of incremental changes to legislation designed to protect consumer interests.

Early in the twentieth century, Harvey W. Wiley, a physician considered to be the “father of the Food and Drug Act” and who served as the first commissioner of what would become the Food and Drug Administration, worked to institute consumer protections.

In the 1990s, during his tenure as FDA commissioner, David Kessler '77 took up the cause of consumer advocacy by establishing the Nutrition Facts food label mandated by the Nutrition Labeling and Education Act of 1990.

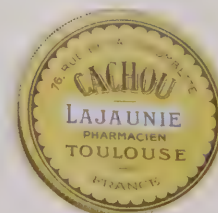
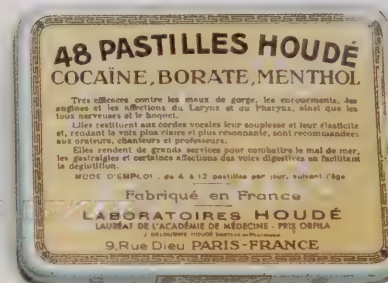
Now, the current commissioner, Margaret Hamburg '83, is overseeing a redesign of this label, an update intended to further aid consumers who wish to make better food choices in the supermarket. —Susan Karcz





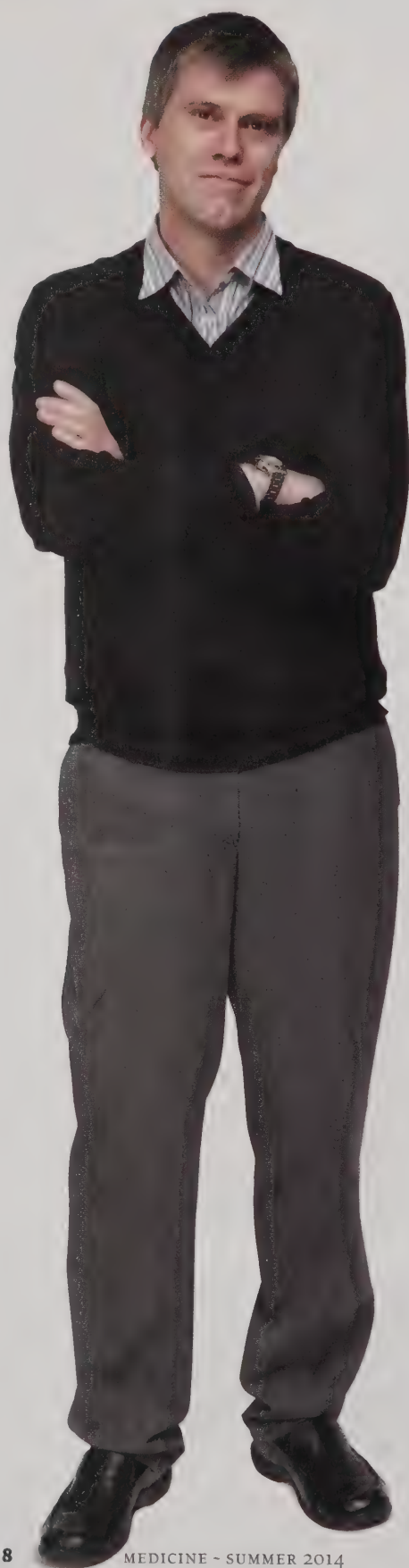
TIN TYPES: Objects include tins containing pastilles, cachets, lozenges, laxative pills, and salves; and cigarettes that purport to promote easier breathing.

From the William H. Helfand Collection in the Center for the History of Medicine at the Francis A. Countway Library of Medicine.



FIVE QUESTIONS

FOR ULRICH VON ANDRIAN



What prompted you to become a physician-scientist?

I grew up in Munich and, as a youngster, my interests were more in playing soccer and tennis and having fun. I was not an excellent student. But I always was intrigued by science.

My godfather, who was a vascular surgeon in Munich, told me about the Institute for Surgical Research. It was like walking onto the set of *Star Trek*. There were rooms with fancy things they called computers, which were not really commonplace at the time. I thought to myself, I want to do something really amazing here.

What drew you to immunology?

One organ that is not definable by its location is the immune system. This makes perfect sense because this system has evolved to attack infections that can occur anywhere in the body, and its forces must be deployed wherever they are needed.

The ubiquity of this system has always fascinated me. My early years in science were spent trying to understand how white cells in the bloodstream get pulled into tissues, how you make this process efficient, how you make it specific, and how it may explain some of the interactions you see not only in response to infections but also in inflammatory and autoimmune diseases.

Did having the ability to create recombinant proteins—the process of cloning—change how you looked at your research?

Learning how to design chimeric molecules was really fun. I remember looking through the microscope at fluorescent cells expressing a protein that I had made, one

**The Edward Mallinckrodt Jr.
Professor of Immunopathology,
Harvard Medical School**

that hadn't been conceived by nature. This amazing ability to harness the principles of nature to do things that come out of your mind was spectacularly cool.

Did you have a mentor when you were a young researcher?

I consider Karl Arfors, a recognized expert in inflammation research, to be my mentor. He would repeat a German saying: probieren ist besser als studieren (to try is better than to study). Do a lot of experiments. Acquire data. Try to understand the data and see what you can learn from what comes out on the other end.

I followed his advice and, at one time, thought that some things I did during my early postdoc days seemed rather desperate. Now I think they were some of the most valuable experiences I had.

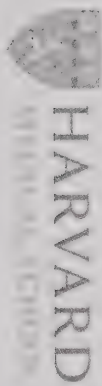
What would people be surprised to learn about you?

I never in my life had a single lesson in real immunology. I was trained as a physician to have a reasonable understanding of how the mammalian body works, how it all hangs together, how one part influences the other parts. I think you need to be able to have the big picture, but then you also need to be able to dig deep and have very high resolution in certain areas.

—Elizabeth Cooney



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THE COMMUNITY OF HARVARD MEDICAL SCHOOL ALUMNI

President's Report



The Alumni Council's 2014 goal was to identify new programs to serve alumni. Your responses to the alumni

interest survey have allowed us to better understand how you wish to interact with the School, each other, and students.

To help address the interest in student mentoring, expressed by many, we are further developing an online community to foster student-alumni connections. We also are developing a marketplace where alumni can share and learn about existing ways to volunteer, such as telehealth opportunities to help the medically underserved.

The alumni relations staff is updating our communications strategy to provide you with more personally relevant and accessible information, starting with a more visible alumni link on the HMS home page. And we are happy to announce upcoming access, through Countway, to several e-journals.

It has been a great pleasure to serve as your Council president this past year and—as a California-based full-time clinician—a privilege to renew connections with the remarkable alumni, staff, and students of HMS.

Laurie Green '76 is an obstetrician and cofounder of Pacific Women's OB/GYN Medical Group in San Francisco.



Vijay Kuchroo

OPPOSING FORCES

Faculty discuss role of immunity and inflammation in disease and therapy

"IT'S CLEAR THAT IMMUNE-MEDIATED responses are key to diseases not previously associated with the immune system," says Arlene Sharpe '82, the George Fabyan Professor of Comparative Pathology at HMS. Reunion Week's faculty symposium, held May 29, presented some discoveries that are illuminating the role that chronic inflammation plays in cancers, allergies, inflammatory bowel disease, neurodegenerative diseases such as multiple sclerosis, and metabolic diseases such as diabetes.

There's been a troubling rise in obesity over the past 20 years, which, according to the panelists, has paralleled increases in cardiac and metabolic diseases and in type 2 diabetes. Diane Mathis, the Morton Grove-Rasmussen Professor of Immunohematology at HMS, notes that chronic low-grade inflammation underlies

these diseases. She spoke in particular about the inflammatory aspects of obesity. Her lab found that regulatory T cells, which help control almost all immune responses, are missing in the adipose tissue of an obese person. "We have found a factor that helps regulatory T cells establish themselves," says Mathis, adding that increasing this factor in people who are obese may help them avoid the chronic conditions associated with obesity.

Recent research has also unraveled some of the mysteries of inflammatory bowel disease, reports Ramnik Xavier, the Kurt J. Isselbacher Professor of Medicine in the Field of Gastroenterology at HMS and chief of the gastroenterology unit at Massachusetts General Hospital. Scientists now know the genetic factors that contribute to the disease and the important

role that gut bacteria play. "Many of the genes associated with Crohn's," says Xavier, "are responsible for the immune system's recognition of microbes." His lab found that Crohn's disease and ulcerative colitis have microbial "signatures"—a balance of "good" and "bad" bacteria that are condition-specific—that also indicate disease severity.

After a century of unfulfilled promises, "I think immunotherapy is ready to change the face of cancer therapy," says Gordon Freeman, an HMS associate professor of medicine at Dana-Farber Cancer Institute. Stimulating immune response hasn't worked, but blocking inhibiting pathways has. His lab discovered two interacting protein molecules that affect T-cell function, and found that cancer cells "learned" to express the protein that inhibits immune response. Treatments that used antibodies to that protein decreased tumor size and stopped tumor growth for years.

Vijay Kuchroo, the Samuel L. Wasserstrom Professor of Neurology at HMS, studies autoimmunity and tissue inflammation and discovered TH17, a pathogenic T cell. TH17 is present in inflamed tissue, including in multiple sclerosis lesions in the brain. A clinical trial of an anti-TH17 drug showed a significant decrease in the number of MS lesions in the brain. His research team also found cytokines that make T cells pathogenic. Kuchroo's group also has investigated salt's effect on the immune system and its role in inflammatory bowel disease.

A video of the symposium may be viewed at hms.harvard.edu/reunion/2014-recap.

—Ellen Barlow

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THE COMMUNITY OF HARVARD MEDICAL SCHOOL ALUMNI



FILM INDUSTRY

Forging 'living' materials in a biofoundry

BIOFILMS ARE LIVING FACTORIES. These slicks of bacteria can harm humans when they cause stubborn infections. Yet biofilms have other properties, remarkable ones, such as their ability to respond to their environments and to exhibit heterogeneity across nearly all measurable parameters—chemical, structural, electrical, and physiological—that synthetic biologists such as Tim Lu '10 would like to exploit.

Lu, an associate professor of biological engineering and electrical engineering at MIT, wants to integrate the best of the living and nonliving worlds into biofilms. His team of researchers has been moving in that direction and has recently successfully combined biofilms, composed of the bacteria *Escherichia coli*, with gold nanoparticles and with quantum dots. Gold nanoparticles allow the cells to conduct electricity while quantum dots allow them to emit light. The work is reported in the May issue of *Nature Materials*.

Biofilms assemble themselves into multicellular materials that grow, sense their environments, and adapt to them. These characteristics suited Lu and his team; they wanted cells that could organize materials on a small scale, a large scale, and all scales in between. The scientists also wanted to control when these biological foundries would begin producing materials. And they wanted cells that naturally communicate with one another, so that the cells could send and receive messages about the functional materials being formed. Biofilms satisfied these spatial, temporal, human, and autonomous control specs.

With these specifications in mind, Lu recruited *E. coli*. These bacteria have chains of amyloid proteins, known as curli fibers, that can grow long and thin over scales that range from the nanometer to several microns.

When the scientists tagged the curli fibers with bits of protein called peptides, the fibers became versatile enough to grab onto gold particles, transforming themselves in electricity-conducting nanowires. The scientists also grew quantum dots, which are light-emitting nanocrystals, by capturing the zinc and sulfur that had been fed to the bacteria. Zinc and sulfur are minerals typically found in semiconductor materials.

For now, adding such chemicals to biofilms is the way Lu's team controls the process. The next goal is to use light to activate different circuits that switch individual genes on and off.

"The systems we have are nowhere near as complex as natural biology can be," says Lu. "Our fantasy is to grow something like bone or enamel. This is a first step to show it's possible."
—Elizabeth Cooney

ASSEMBLY LINE: Allen Chen (left) and Tim Lu are key members of the research team that developed hybrid biofilms. Chen is a student in the Harvard-MIT Health Sciences and Technology Program in Lu's lab.



Ethics Evolution

Division of Medical Ethics becomes the Center for Bioethics

TO HELP CAREGIVERS AND RESEARCHERS prepare for the ethical questions that arise in the rapidly evolving disciplines of biomedicine, HMS is transforming the Division of Medical Ethics into the Center for Bioethics.

"The HMS community is home to world-class thinkers about the ethical dimensions of new discoveries and new ways of delivering care," says Jeffrey S. Flier, HMS dean. "In this time of extraordinary change and rapid advances in biomedical science, bringing together leaders from throughout our community into the Center for Bioethics

will provide a crucial focal point for these discussions."

The center will bring together faculty who will collaborate with ethics services at the HMS affiliates and with ethics programs at schools throughout Harvard University. Center faculty also plan to develop a new master's program in biomedical ethics. It is expected to welcome its first class in the fall of 2015.

Robert Truog, an HMS professor of anaesthesia (pediatrics) at Boston Children's Hospital, has been named director of the center. Truog has had a

leading role in the medical ethics division for 10 years.

Truog will continue his clinical work in pediatric critical care medicine at Boston Children's, where he has practiced for more than 25 years, including a decade as chief of the Division of Critical Care Medicine. He is also director of the Institute for Professionalism and Ethical Practice at Boston Children's and chair of the Harvard Embryonic Stem Cell Research Oversight Committee.

Edward Hundert '84, a psychiatrist, previous associate dean for student affairs at HMS, and the School's incoming dean for medical education, will serve as associate director of the center. Hundert currently serves as senior lecturer in medical ethics and director of the medical ethics and professionalism curriculum. He will have a leading role in developing the new master's program.

Christine Mitchell, a registered nurse who specializes in clinical ethics, will be the center's executive director. In addition to developing and managing the ethics program at Boston Children's for the past 30 years, Mitchell has helped to develop ethics education programming for clinical and research faculty across HMS and its affiliates. —Jake Miller

Science Matters

WHAT MOTIVATES RESEARCHERS to spend their lives pursuing answers to difficult questions? For some, it's the thrill of discovery. For others, it's the collaborations formed along the way. The *Science Matters* series of 60-second videos explores the work of the HMS faculty and alumni who are behind the discoveries that are shaping biomedicine.

Margaret Livingstone, professor of neurobiology, is one of the scientists featured in the series. "The brain is a fantastically complex organ," Livingstone says. "I can't imagine anything more exciting or interesting to study."

To watch Livingstone and other HMS researchers as they explain what they do, why they love it, and why it matters, visit hms.harvard.edu/research/science-matters.



Margaret Livingstone

CLASS NOTES

NEWS FROM ALUMNI

1948

J. Gordon Teter

I retired about two years ago after 52 years as a practicing surgeon. My wife, Mary, and I have rented a house next door to our daughter Sarah, and are grateful for reasonably good health.

1954

Arthur Garceau

I am well, and I appreciate all of

you more fully now than ever. I've had a few falls and experience gaps in memory and a few other old age glitches. This medical school and its people, especially you, my classmates, have been the major inspirations of my life. I am proud to be one of you.

1956

John Grover

I am sorry to see our class struggling to avoid falling off the edge of the earth! I especially miss

Joel Alpert, and welcome Norm Levine and Steve Schatzki to fill his shoes. My preoccupation with music keeps me going.

1957

William B. Greenough III

The American Geriatrics Society has awarded me the Arnold P. Gold Foundation Humanism in Medicine Award.

John Parker

In honor of our leadership in es-

tablishing the Clinical Cytometry Society (now the International Clinical Cytometry Society), pathologist Mariano La Via and I have been honored with a plenary session named for us. The first of these sessions was held at the 2013 Annual Clinical Cytometry Meeting.

1958

Elliott Miller

Liz and I are moving to Highland Green in Topsham, Maine, this summer. **Tony Patton** and his wife, Chris, already live there!

1961

Royce Moser Jr.

My term as immediate past president of the Harvard School of Public Health Alumni Association concluded last fall. I also served as president of the HSPH Alumni Council from 2009 to 2011, and as a councilor since 2003.

Robert West

In April, I published *It Can (and Does) Happen Here!: One Physician's Four Decades-Long Journey as Coroner in Rural North Idaho*. This book is my perspective on the coroner/medical examiner system. Although I am retired, I continue to seek remedies for our fractured death-investigation system.

1964

Rob R. MacGregor III

Peggy and I celebrated our 50th wedding anniversary this year. We married on June 10, and I started my internship on June 24! We felt that the only thing worse than getting married just before internship was



not getting married then! She has been very patient ever since.

1970 **45th** REUNION

Thomas Anderson

I have been an active member of the Illinois State Medical Society since 1975 and was elected vice president at its annual meeting in June.

I recently served as a trustee and am currently a member of the society's Council on Economics.

1971

Kenneth Dardick

July marked the 38th anniversary of my medical practice in Storrs, Connecticut. I remain busy in direct patient care for many of my second- and third-generation patients. Our group gave up hospital inpatient care two years ago, which I mourn greatly. I still, however, make house calls.

I've also conducted research on Lyme and other tick-borne infections. This work on *Babesia* epidemiology and the newly identified *Borrelia miyamotoi* has resulted in three publications this year.

I recently visited Ho Chi Minh City, Vietnam, where I supervised the Certificate in Travel Health exam for the International Society of Travel Medicine. I am the chair of the examination committee. It is clearly better to create and supervise an exam than to sit for one!

I also note with sadness the passing this past year of Joel Alpert '56, an important mentor of mine at the Harvard Family Health Care Program. It was Joel who, while leading attending rounds one day at Boston Children's Hospital, responded to the complaint of

the house staff that they had "no good patients to present—too many empty beds," by saying, "let's talk about empty beds—maybe we should consider that an accomplishment. If kids are healthy they won't be in the hospital."

David Lebwohl

I have retired from my nephrology practice and now spend winters in Key West.

1973

David Lee

I still believe in primary care and am still practicing in Boise, Idaho, a wondrous community.

1974

Richard Sims

I am professor emeritus at the University of Alabama School of Medicine and am semiretired from primary care practice at Cooper Green Mercy Hospital in Birmingham. I have been married for 32 years to Michele Jean. Our daughter, Alexis, is an actress; our son, Matthew, works in food service.

1978

Jeffrey Bernhard

The board of directors of the International Forum for the Study of Itch has established the Jeffrey D. Bernhard distinguished lectureship, which will be offered biennially at the World Congress

on Itch. The first Bernhard lecture was delivered at the World Congress in September 2013. I am now professor emeritus and former chief of dermatology at the University of Massachusetts Medical School, and editor emeritus of the *Journal of the American Academy of Dermatology*.

1982

Aaron Appiah

I'm still practicing vitreoretinal surgery in sunny Florida.

1983

David Keller

I left New England for Denver and became vice-chair for clinical affairs and clinical transformation



CLASS NOTES

NEWS FROM ALUMNI



at Children's Hospital Colorado. Mt. Harvard is not far away. Come visit!

1984

Amy Billett

After years of being active in the American Society of Pediatric Hematology Oncology (ASPHO), I was honored to start my term as vice-president of the board of trustees at the annual meeting in May. ASPHO was founded in 1981 to promote research and treatment for children and adolescents with cancer and blood disorders, and has been an incredible resource and support throughout

my career as a pediatric oncologist at Dana-Farber/Boston Children's Cancer and Blood Disorders Center. The vice-president of ASPHO also serves as president-elect, so once my term ends in 2016, I will begin a two-year term as president.

1986

May Reed

I biked the White Rim Road at Canyonlands National Park with Bill Lindsey last year. I look forward to biking the North Rim of the Grand Canyon with Bill, Greg Pearson, and Mary Ann Schran this year!

1997

Ceasar Valle

I'm serving my 14th year as an active duty Air Force pediatrician and flight surgeon. I currently serve as the chief of the medical staff at Los Angeles Air Force Base. Stephanie and I are busy raising our four children and have enjoyed the travels the service has entailed thus far.

2006

Elizabeth Guancial

I accepted a position as an assistant professor of medicine and oncology at the Wilmot Cancer Institute, University of Rochester, New York.

Share Your News

If you have updates you'd like to share in Class Notes, you can now submit them easily and securely to class-notes@hms.harvard.edu. Be sure to include your full name and class year.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1940s

1942

Carrington Williams
March 30, 2014

1943

John Burbank
June 24, 2014

1944

Alfred Jaretzki III
May 29, 2014

Edward P. Wallace
July 4, 2014

1945

Judson S. Griffin
June 14, 2014

1947

B. Hughes Kennedy III
March 15, 2014

1948

Kenneth Fremont-Smith
June 16, 2014

Thomas J. Vecchio
June 4, 2014

1949

Donald L. Fry
May 6, 2014

Frederick A. Peirce Jr.
March 30, 2014

1950s

1950

Donald C. Borg
April 15, 2014

Melvin J. Glimcher
May 13, 2014

1951

Robert L. Early
March 5, 2014

James K. Greenbaum
March 13, 2014

1952

John F. Bertles
April 6, 2014

Henry U. Grunebaum
April 11, 2014

1953

Stanton V. Huffman
April 3, 2014

1954

Mitchell S. Karlan
April 24, 2014

Milton L. Levine
July 10, 2014

1955

William Bolman
April 18, 2014

William S. Fletcher
July 12, 2014

George L. Harper
April 8, 2014

Charles S. Keevil Jr.
April 8, 2014

1956

Frederick L. Dunn
May 24, 2014

Oscar A. Iseri
April 25, 2014

1958

Richard C. Hutchinson
July 8, 2014

Karl H. Wegner
April 4, 2014

1959

Oscar A. De La Cruz
July 6, 2014

1960s

1960

Arthur Bank
February 27, 2014

1961

Fenwick C. Riley Jr.
April 20, 2014

1963

James T. Ogilvie
July 11, 2014

1964

Stanley E. Shackney
July 13, 2014

William T. Thach
July 1, 2014

1967

Miriam D. Mazor
April 4, 2014

Richard S. Shulman
March 21, 2014

1970s

1971

James G. Sise
January 26, 2014

1976

Gerald M. Sloan
May 20, 2014

1979

Richard G. Rockefeller
June 13, 2014

This listing of deceased alumni and their dates of death include those alumni whose notices of death were received between March 8, 2014, and July 25, 2014. Links to full obituaries of these alumni can be found at hms.harvard.edu/memorial.

If you know of an HMS alumna/us who has died recently, please send an email with the link to the obituary to hmsalum@hms.harvard.edu.

TAKING A HISTORY

PROFILE OF RITA CHARON



CLAIMS TO FAME
Professor of Medicine, Columbia University Medical Center; director of the Program in Narrative Medicine, Columbia University College of Physicians and Surgeons; author, *Narrative Medicine: Honoring the Stories of Illness*.

GENERATIONAL TALE

Rita Charon '78 is a third-generation physician. Her grandfather practiced in Chamblay,

near Montreal, before moving to Manville, Rhode Island; her father saw to the medical needs of a French-Canadian community in Providence, where she grew up. According to Charon, "They were both kind of small-town, general practitioner, all-around country doctors," who delivered babies and performed minor surgeries.

Charon took time off between college at Fordham University and medical school at HMS to participate in antiwar politics and teach in a New York City school. After a few years, however, the family's profession began to tug at her. "I'd always thought my father's idea, that I should become a doctor, was a pretty good one, so I returned to that."

Her father continues to be a role model. "I have all of his medical charts. I read them and rediscovered what kind of doctor he was. His work has helped me be the doctor I am."

WORDSMITH

It was at HMS that Charon found her mentor: Elliot Mishler, a sociologist and linguist who is now an HMS professor of social psychology at Cambridge Health Alliance. Working with Mishler, Charon grew to understand how doctors and patients use language to teach each other.

This budding interest in language led Charon down a new path. After completing her training in primary care, she joined the faculty at Columbia University College of Physicians and Surgeons. There, she was struck by the power of patients' stories. She began taking courses in Columbia's English Department, where she eventually earned a doctorate.

FIRST EDITION

Charon merged her passion for medicine and language: She introduced narrative medicine into medical education. Since the 1980s, she has taught classes and led workshops in this field for both students and faculty.

The narrative medicine program she directs at Columbia encourages medical students to enter official assessments on patients' hospital charts and, on parallel charts, to write feelings about and reflections on the patients. This separate effort is designed to foster empathy. First-year medical students must also produce a portfolio that includes their reflections on becoming a physician. "Writing," Charon says, "is discovering."

In 2009, Charon and her colleagues admitted their first students into Columbia's Master of Science in Narrative Medicine.

STORY ARC

Charon continues to practice primary care at New York-Presbyterian Hospital, where she has been since 1981. "Some of these patients have had me as their doctor for 33 years," she says.

Charon believes that an appreciation of the role of language helps a physician listen to patients' stories, share their own stories, and reflect on the human connections those stories form.

"We call ourselves narrative medicine now, which is, I think, a pretty good description of what it is. More and more of us are bringing this literary narrative sophistication into clinical routines," she says. "This sensibility has made me into a very different kind of doctor from what I was when I started."

—Katie DuBoff



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